REFILLING MECHANISM TO STABILIZE A FREE-FLOATING INTRAOCULAR CAPSULE DRUG RING

by

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STATEMENT OF THESIS APPROVAL

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ABSTRACT

This work discusses several ways to grab and refill an intraocular drug device targeting age-related macular degeneration (AMD). The capsule drug ring (CDR) is an implantable device that stores and releases drug inside the lens capsule. Since an intraocular lens (IOL) is placed in the lens capsule during cataract surgery, a CDR can be put on the unused periphery between the IOL and the lens capsule. The objective of the refilling mechanism is to stabilize a free-floating CDR to allow penetration through the refilling ports. Two ports at each end of the CDR allow the reservoir to be refilled with bevacizumab (Avastin) every six months to one year. Some mechanisms are added on the CDR to achieve a refillable CDR.

Several grabbing mechanisms are discussed and tested in this work. The 23-gauge refilling device includes a 30-gauge needle, used to penetrate the ports and inject Avastin into the CDR reservoir. Grasping, vacuum tubing, and lasso devices have been tested to stabilize and refill the CDR: These three concepts were compared and chosen to explore the possibilities of the superior lasso device. Therefore several lasso devices were tested and simplified for use. Finally, possible future modifications to the refilling devices are discussed.

TABLE OF CONTENTS

LIST OF FIGURES

Figure Page

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CHAPTER 1

INTRODUCTION

1.1 Introduction to Human Eyes

The human eye is a complex structure. It consists of mechanisms to sense and visualize incoming light. Figure 1.1 shows a schematic diagram of a human eye.

For a person to see an object, light from that object has to pass through the pupil on the lens capsule and focus on the retina. Light focused on the retina sends electrical signals to the brain, which in turn forms an image of these signals. The central area of the retina is called "macula," which is about 10% of the retinal area. The central part of the macula is called the "fovea". Though the entire retina can sense incoming light signals, most of the central vision relies on the signal received at the macula and fovea [2].

1.2 AMD and Its Treatment

AMD is the loss of central vision due to macular degeneration. Depending on the cause and history, it can be divided into two categories: dry AMD and wet AMD. AMD always starts in the dry form, and for some patients it will become the wet form. Dry AMD is what happens when the light-sensing cells of the macula die much earlier than normal, and therefore the light focused on specific spots of the macula cannot be detected. This produces a blur or incomplete image. On the other hand, wet AMD is caused by the new vessel growth in the vitreous humor. The growth of the neovessels is called

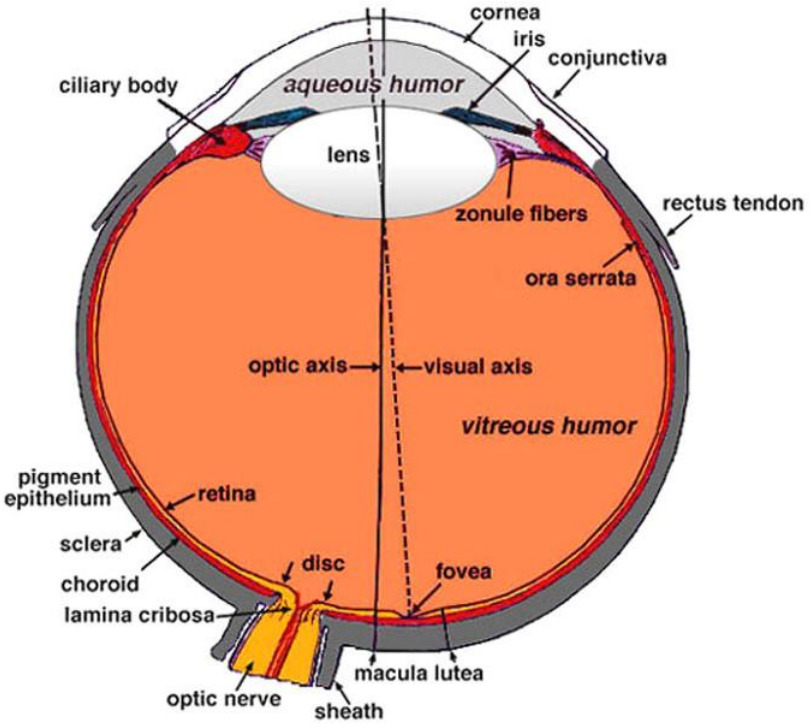


Figure 1. 1 Schematic diagram of the structure of a human eye [1]

"angiogenesis." These neovessels will leak liquid or blood under the macula, or even fovea, and thus either swell or damage the macula and distort vision. Ten percent of patients with dry AMD will develop wet AMD [2, 3].

Currently, there is no direct treatment for dry AMD. Some ophthalmologists will recommend that patients with advanced dry AMD consume high dose of zinc and antioxidants. This treatment is referred to as "Age-Related Eye Disease Study (AREDS) formulation." On the other hand, contemporary treatment for wet AMD includes photodynamic therapy with Visudyne, Macugen injection into the vitreous humor and macular translocation surgery. The drawbacks for these treatments are hypersensitivity to light, constant visits to perform vitreous injections, and the high risk of vitreous surgery. The drug for AMD treatment is Avastin, which blocks the vascular endothelial

growth factor (VEGF), a chemical signal which promotes blood vessel proliferation.

The capsule drug ring (CDR), which was recently developed at the University of Utah, targets wet AMD and slowly releases Avastin over a period of six months to a year to hopefully reduce the need for monthly vitreous injections of drugs. In CDR treatment, the initial macula surgery is followed by cataract surgery. An intraocular lens (IOL) is placed in the lens capsule after cataract surgery to replace the original lens capsule gel. Because the IOL is smaller in diameter than natural lenses, there is unused space around the IOL. The CDR is placed between the wall of the lens capsule and the IOL. Figure 1.2 shows a sketch of the CDR and the IOL inside an eye [4].

1.3 Capsule Drug Ring Systems

The Capsule Drug Ring (CDR) can be implanted by an ophthalmologist during or after the cataract surgery. The CDR is a device that stores and releases drug inside the

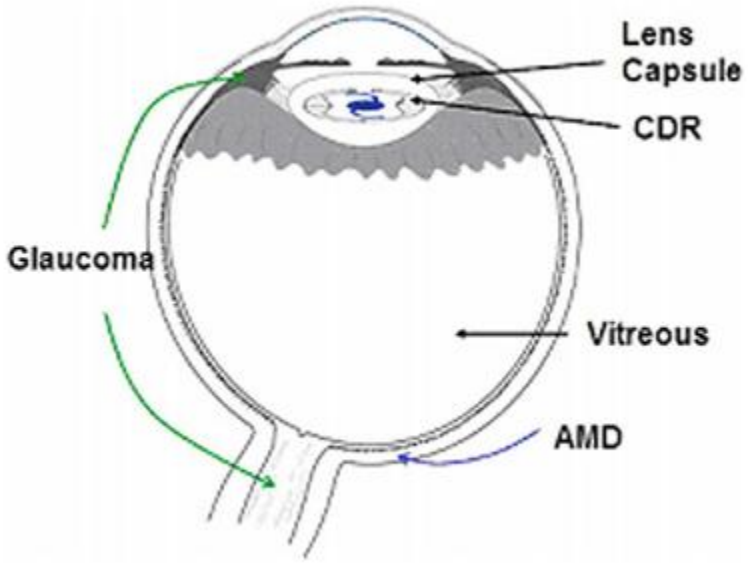


Figure 1. 2 Sketch of a CDR and an IOL inside an eye [4]

capsular bag. In the early design stages of the CDRs, two silicone valves served as injection ports (Figure 1.3, left). Later, a reservoir made by polycarbonate-based polyetherurethane, commercially known as "Carbothane," was tested, to fill both the structural and the filling-port functions (Figure 1.3, middle). Additionally, a membrane made of polyethersulfone (white), was built into the CDR to allow drug to diffuse into the eye. In this project, similarly-fabricated CDRs were developed by me, but the CDRs are compatible with lasso-based refilling devices (Figure 1.3, right). These devices will be described in much more detail throughout this thesis.

1.4 Comparison of Refillable Drug Carriers with Dissolved Drug Capsule

The CDR is a refillable drug carrier which can last for at least six months per refill. The advantage of a refillable drug carrier is that it can be used repeatedly and without risk of the structure dissolving away or contaminating surrounding human tissue. However,

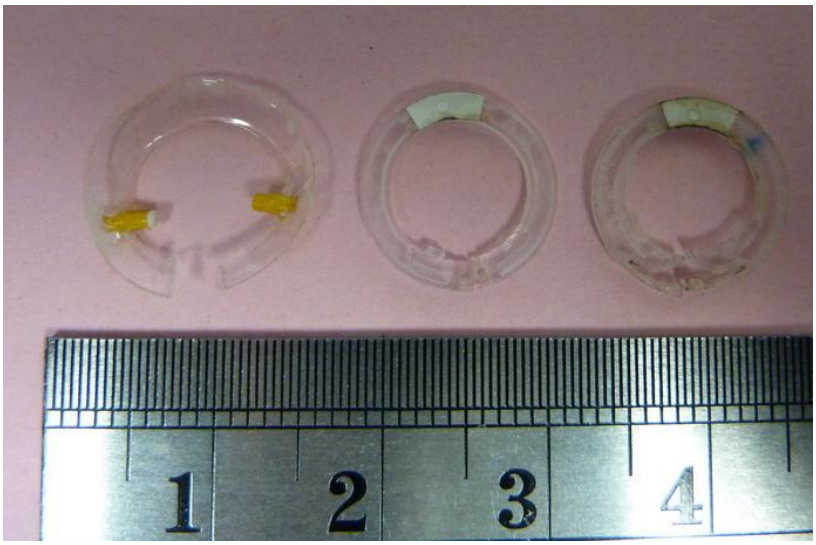


Figure 1. 3 List of CDRs
(Left) The first prototype CDR. (Middle) A CDR with Carbothane ports.
(Right) The lasso-based CDR.

the cleanliness of any reused device must somehow be guaranteed through careful inspection, following each refilling surgery. Also, the refilling process presents a challenge, as the drug must be accurately injected into the capsule without leakage and without damaging the delicate structures in the eye.

A proposed variant of the implantable CDR is a resorbable drug ring that could be implanted and would slowly release drug as it dissolves. With a resorbable or dissolving drug capsule, on the other hand, a new drug ring is implanted every six months or a year through a careful surgical procedure that minimizes the possible contamination of the lens capsule. A dissolving drug ring has its own challenges. If the drug ring dissolves into small membranes in the lens capsule, it might become an artificial cataract and block some vision. Besides, if some parts of the capsule start to dissolve before the end of the dose period, the drug might leak into the lens capsule, dramatically raising the drug delivery rate, which can be problematic. As the resorbable device is not yet practical or actively in development, this thesis will focus on the refillable CDR.

1.5 Design Rules for Refillable CDRs

The primary objective of this project was to develop and implement a technique for refilling a CDR that was practical and efficient. The complete CDR system will require both a CDR and a tool for refilling the CDR, and the two components must be compatible. This section focuses on the CDR itself, while the following section discusses the tools for making the injection. The design rules for the refillable CDR are divided into two categories: materials and dimensions.

The materials used in refillable CDRs have to be stable and insoluble *in vivo*. The structural material has to be scratch-resistant, as it will come in repeated contact with the

sharp refilling needle; it also must be self-sealing after receiving a puncture hole, to stop the stored liquid from seeping out of either pin-prick injection port, following withdrawal of the hollow filling needle.

The dimensional constraints are the outside and inside dimensions of the annular-shaped CDR. Since the CDR is placed between the IOL and the lens capsule, its inside diameter should be greater than the IOL's, and its outside dimensions are limited by the space provided by the lens capsule. The CDR is placed into the eye via two 3 mm incisions. The maximum thickness dimension of the CDR is found to be 1.2 mm. Dimensional limitations will be discussed further in Section 2.1.

Above all, the engineering specifications of the CDR are listed below:

1. Biocompatible materials.
2. A sealing drug reservoir.
3. Dimensional limitations.
4. Compatibility with and without a filter.
5. Self-sealing ports.
6. Eyelets.
7. (Optional) Mechanisms to interact with grabbing and refilling devices.
8. Reasonable volume of the drug reservoir.

1.6 Design Rules for Refilling Tools

The tools used to refill the CDR after six months or a year in the eye must be specifically designed to be compatible with the CDR and with standard ophthalmic surgeries. Accordingly, the CDR will be placed into the lens capsule through a 3 mm incision in the cornea. The same incision is used for a refilling tool to be placed in the

lens capsule to inject the drug into the reservoir in the CDR. A tool with a thickness no greater than 23 gauge (outer diameter is 0.025 inch, or 0.635 mm) is the maximum allowed based on past ophthalmologist experience, even though it is much smaller than the 3-mm long incision. When entering the incision, no sharp protrusions can be presented to prevent potential risk to the eye.

A refilling device must be able to grab the CDR tightly and pull it against the sharp point of the refilling needle until connection to the reservoir is made, with minimal displacement of the CDR inside the eye. The liquid inside the drug reservoir of the CDR has to be removed first, and then the drug can be injected into the CDR. This device also needs to be operated easily. The actual drug injection needle is limited to a 30 gauge size. Eventually all these processes should be as automated as possible, so that the refilling, injection, and removal processes are as repeatable as possible with minimal effort on the part of the doctor.

All parts of the refilling device to enter the eye must be sterilized and be made of biocompatible materials. Also, these parts can be disposable and replaced after each surgery.

Above all, the engineering specifications for the refilling tools are listed below:

1. Biocompatible materials.
2. 23 gauge outer sheath with 30 gauge injection needle.
3. Prevention of scratch to the lens capsule.
4. Firm grabbing.
5. Prevention of CDR rotation while pricking.
6. Maximum feature size smaller than 1.6 mm.
7. Self-recovery nitinol loop before refilling.

8. Ability to flip the CDR into the same plane as the grabbing device.
9. (Optional) Self-recovery nitinol loop after refilling.
10. Automatic control of grabbing and refilling.

1.7 Summary of Thesis

The current chapter has described the structure of the human eye and AMD, an eye disease that is expected to be treated using a CDR. Engineering specifications for refillable CDRs and refilling devices were discussed as well. Chapter 2 will illustrate the design of the CDRs and functions of their components. Chapter 3 will address the various aspects of testing the CDRs. Chapter 4 will go into the design details of lasso grabbing mechanisms. Chapter 5 will present the result of testing the lasso grabbing mechanisms. Chapter 6 will introduce other grabbing mechanisms and CDRs. Chapter 7 will give our conclusions and will point out future improvements for both the CDR and the grabbing device.

CHAPTER 2

DESIGN OF CAPSULE DRUG RINGS

The purpose of the CDRs discussed in this thesis is to release Avastin or related drugs intraocularly for at least six months without refilling, but at the end of that time, they must be refillable, as they will be difficult to remove and replace.

There are two overarching issues for the initial design of the CDR: the biocompatibility and the drug delivery rate. Biocompatibility is important since the CDR will reside inside the lens capsule for a long time; therefore, not only should the materials of the CDR be harmless to the human body, but the human immune system must not attack or reject the CDR.

The second issue, constant drug delivery rate, is crucial for any drugs to function properly and the treatment to be effective. If the intraocular concentration of the drug is too low, it cannot produce effective therapy. If the intraocular concentration of the drug is too high, it will become toxic to the human body and lead to negative side effects. A constant diffusion rate of the drug out of the CDR makes it possible to achieve a constant intraocular drug concentration. Over time, the drug delivery rate from the CDR will fall as the drug in the CDR is depleted, which necessitates refilling of the CDR to keep the drug delivery rate at appropriate levels. This drug delivery rate cannot be negatively impacted by the refilling process, either by introducing leaks that increase the delivery rate or by failing to fully fill the device, which will lead to premature depletion of the drug and a loss of drug delivery.

Before this project began, prototypes of a CDR had been developed, and methods for refilling the device had been implemented, but they were found to be limited because the needles could not be pressed through the valves in the CDR as there is little mechanical resistance inside the lens capsule, so the CDR was essentially "free floating." Thus, it was determined that a method for grabbing and holding the CDR was needed if a successful injection was to be made. The task of grabbing, holding, and injecting drug into the CDR is the focus of this project.

2.1 Dimension Limitation

The CDR is placed into the space between the IOL and the lens capsule after cataract surgery. The inside dimensions of the lens capsule may be described by that of an inscribed disk, 15 mm in diameter and 5mm in thickness, such that, allowing for clearances, each CDR should be no larger than 13 mm in diameter and 2 mm in thickness. We decided to stay below these clearances in our design, setting for a CDR dimension of 12.4 mm diameter by 2 mm thick. Only one CDR is implanted in each eye at this point, though it may be able to implant another CDR in the same eye if needed.

Figure 2.1 shows the dimensions of a CDR as presently designed. Most of the dimensions of the CDR were given to me by the ophthalmologist and coworkers who originally designed the device. These dimensions were kept constant throughout this project if possible, though a number of design changes were made, as will be described. The outer diameter of these CDRs is 12.4 mm, and the inner diameter is 8.6mm. The thickness is 1.2 mm for those made of 12 layers of Carbothane sheets, and 1.1 mm for those made by 11 layers of Carbothane sheets. Carbothane is a trade name for polycarbonate-based polyether urethane available in sheet thicknesses of 100 or 50 μm.

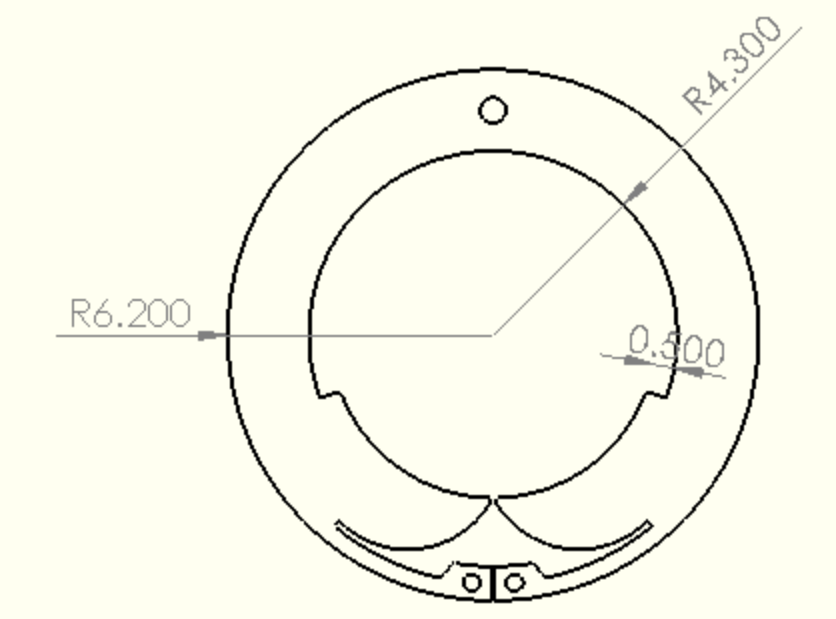


Figure 2. 1 Sketch of a CDR with dimension (Version V21t04)

CDRs might become thicker in the future with the use of balloon structures on the top and bottom walls, all within a stack thickness not exceeding 2.2 mm.

2.2 Design of the First CDR

The first CDR was used to test intraocular biocompatibility and the drug diffusion rate. This research is being conducted by Dr. Himanshu Sant, Nathan Gooch and Michael Burr. In addition, Dr. Sarah Molokhia proposed the initial concepts of the CDR, and Corey Bishop designed the first CDR.

For the fabrication of the CDR, AutoCAD was used to design its geometry and to generate CAD drawings which controlled a CO_2 pulsed-laser planar cutting/engraving machine (model: Universal Versa VLS 3.60). Figure 2.2 shows an AutoCAD drawing of the original CDR and the laser paths used to create the device. Figure 2.3 shows a drawing of the completed device.

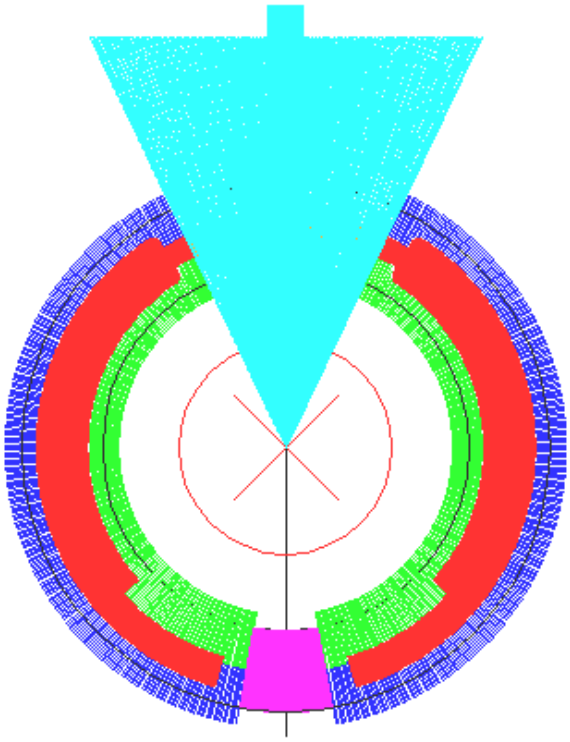


Figure 2. 2 CAD drawing of laser-beam paths of earliest design of a CDR

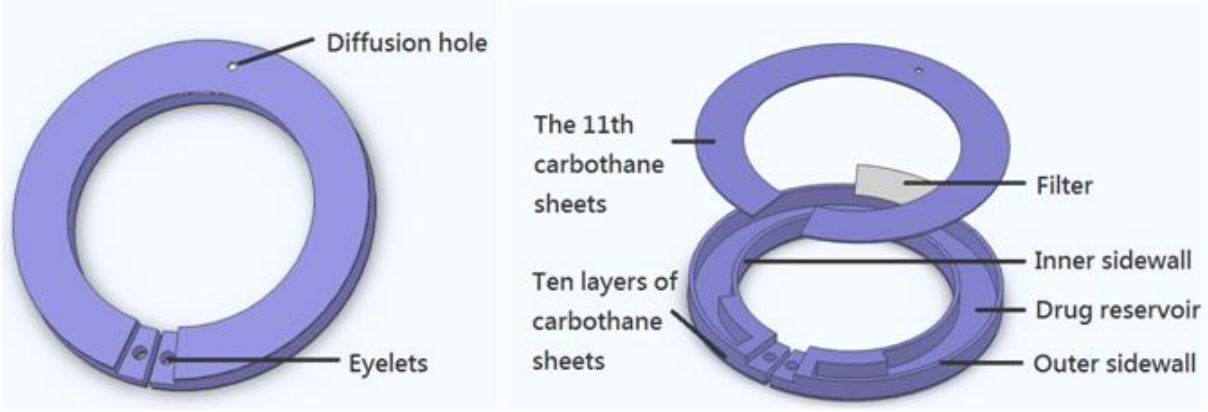


Figure 2. 3 Illustration of a CDR and its dissected view

The fabrication process is performed in nine steps. First, 10 layers of 100-μm-thick Carbothane sheets are rolled flat on top of one another on a glass slide, temporarily held together by surface forces alone. Second, at medium laser power, path identified by the red layer in Figure 2.2, composed of hundreds of radial line segments, were traced by the beam to ablate a 0.8-mm-deep drug reservoir on the 10 layers of Carbothane sheets. Third, at low laser power, radial paths identified by the blue and green lines in the CAD drawing were traced to laminate the 10 layers of Carbothane sheets to one another and to form the inner and outer sidewalls of the CDR reservoir. Fourth, at medium laser power, paths identified by the cyan were traced to etch a cavity for the filter. Fifth, UV-curable adhesive (model: Loctite 4307) is applied to the sidewall of this cavity to attach a similarly shaped polyethersulfone filter membrane to the reservoir, and UV light is applied to that area for three minutes to cure the adhesive used to attach the membrane. Sixth, the same adhesive is applied to the filter area to attach the filter to the eleventh Carbothane layer, to be added in the next step. Seventh, the eleventh Carbothane layer with a small diffusion hole (diameter is 0.6 mm) is rolled flat over everything, and UV light is again applied on that area for another three minutes to cure the adhesive. Eighth, a low-power laser beam is traced, yet again, over the blue and green drawing lines to laminate the eleventh Carbothane sheet to the layers below. Ninth, at high power, the black boundary lines are traced by the laser beam to cut all the way through to the carrier glass slide to release the CDR and to obtain the final product, which is then carefully peeled off the slide.

The thickness of the sidewall is 300 μm by design, and the outer and inner diameters are 12.4mm and 8.6mm, respectively. The measured volume of the drug reservoir is around 18 to 22 μL. Two eyelets at the end of the CDR allow

ophthalmologists to grab the CDR via an IOL injector tool. The IOL injector is designed for placing tension rings in the lens capsule during cataract surgery. As mentioned above, the CDR is placed to surround the tension ring and the IOL after cataract surgery.

2.3 Fabrication Methods

The methods used in Section 2.2 were adapted throughout this project to manufacture a wide variety of CDRs with different geometries and features. The specific manufacturing efforts and techniques are described in this section. Each design iteration of the CDR had its own specifications, as shown in Table 2.1.

2.3.1 Preparation of Thick Carbothane Structural Material

We were unable to obtain Carbothane sheets in the desired thicknesses, so multiple layers or thin sheets were assembled and bounded together to create a starting material with the needed dimensions. The method for producing this thicker sheet is described in the following sections.

The base material for the CDR is a 1mm thick layer of Carbothane. To produce Carbothane in this thickness, either 9 or 10 layers of 100μm thick Carbothane films are rolled flat together, one additional film at a time, on a glass slide. For the earlier stages lasso-based versions (from V1t48 to V9t01 CDRs), nine layers of Carbothane are laminated at low laser power to form the inner and outer sidewalls. The drawbacks of using separate sheets are the time-consuming process and the possibility of leakage due to trapped air bubbles between the layers forming the sidewalls.

The layers of Carbothane are laminated together using heat to form a continuous material. A hot plate is used to heat and press either 9 or 10 layers of 100 μm thick

Table 2.1 Designs of CDRs

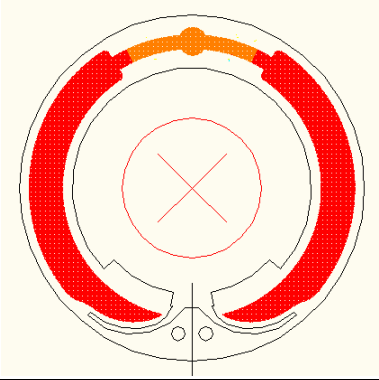
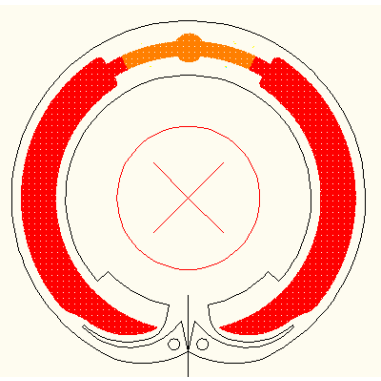
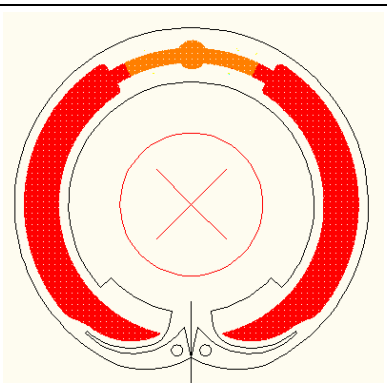
CDR ID	Figure	Design Features
V1t48		Directly changed from initial CDR.
V2t06		1. Trim unnecessary parts of protection walls.
V3t20		1. Smooth the boundary.

Table 2.1 (continued)

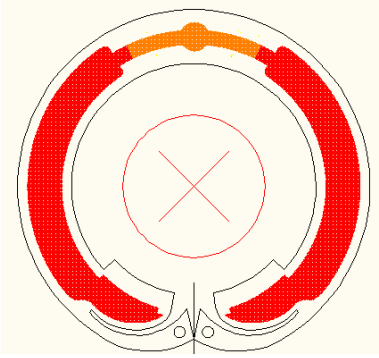
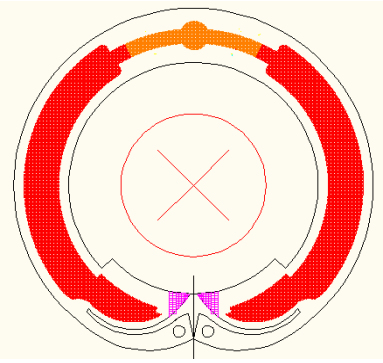
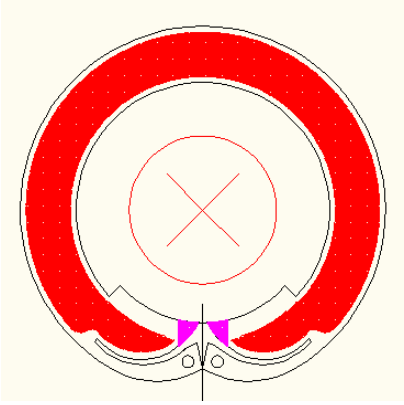
CDR ID	Figure	Design Features
V4t02		1. Increase reservoir by decreasing port thickness.
V5t08		1. Scattered grids at the end to make a tapered entrance for lasso loop.
V6t22		1. Increase reservoir by three-time raster. 2. Increase reservoir by increasing filter area. 3. Increase port thickness to give more structural support during refilling.

Table 2.1 (continued)

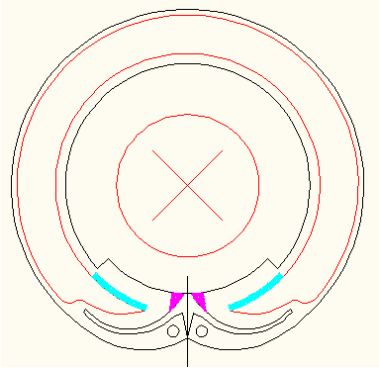
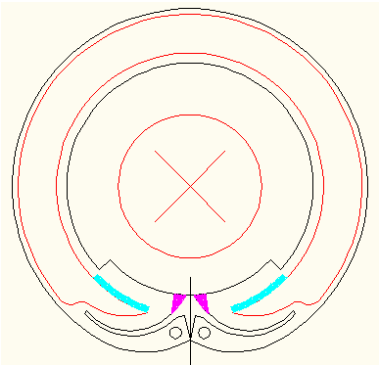
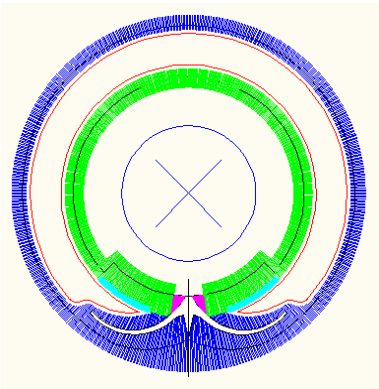
CDR ID	Figure	Design Features
V7t16		1. Clear cut the reservoir. 2. Modification of the scattered grids at the end to prevent leakage. 3. Scattered reservoir at the port area to get balance between reservoir volume and firm structure during refilling.
V8t10		1. Recover the inner sidewall to 300μm. 2. No lamination at lasso guiding gap. 3. Scattered reservoir at the port area to get balance between reservoir volume and firm structure during refilling.
V9t01 Version 1		1. Increase the gap between lamination (green and blue) and the reservoir (red) from 50μm to 150μm.

Table 2.1 (continued)

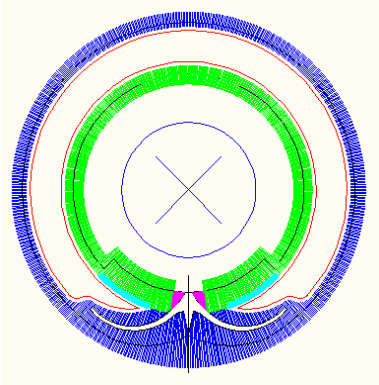
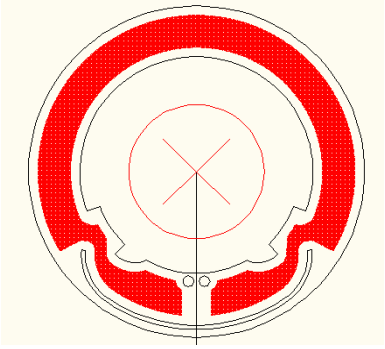
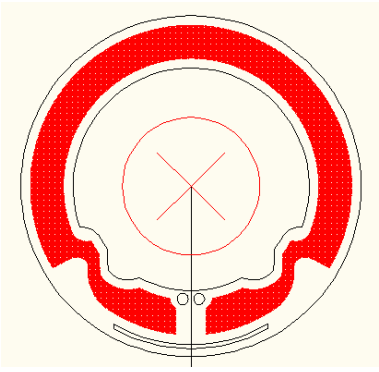
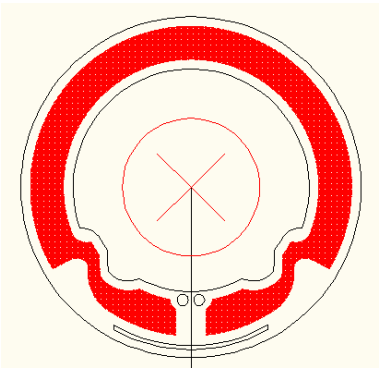
CDR ID	Figure	Design Features
V9t01 Version 2		1. Increase the gap between lamination (green and blue) and the reservoir (red) from 50µm to 150µm. 2. Change parameters of green and blue lamination (lower the power by half) since it is laminated from both sides (top and bottom).
V11t22 Version 1		1. Extend lamination lines (not shown in this figure). 2. Change the guiding gap to the opposite direction 3. Oblique wall on port to balance the rotation while injection.
V12t04 Version 1		1. Shorten the lasso gap to prevent lasso loop going too far inside and changing the angle of injection.
V12t04 Version 2		1. Shorten the lasso gap to prevent lasso loop going too far inside and changing the angle of injection. (The difference between V12 Version 1 and 2 is the time for black final cut.)

Table 2.1 (continued)

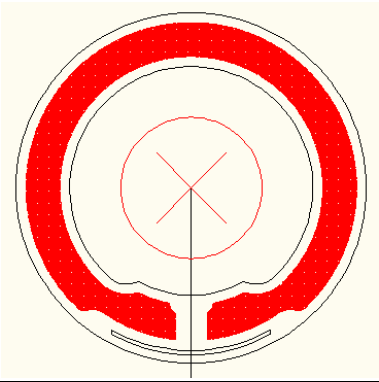
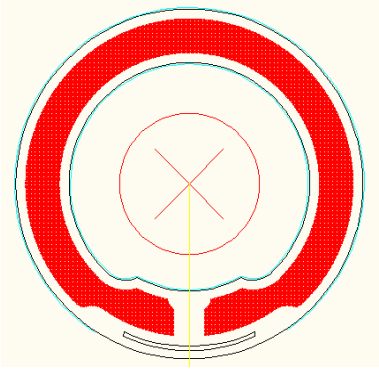
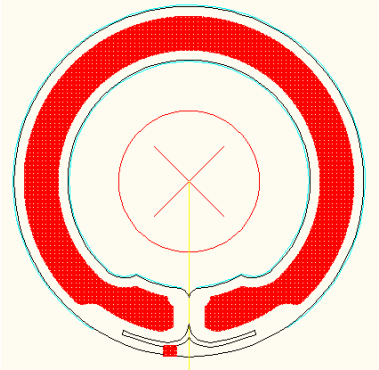
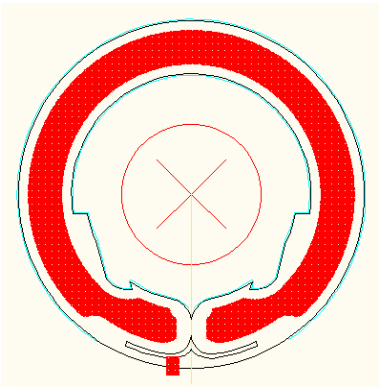
CDR ID	Figure	Design Features
V13t09		1. Increase reservoir in unused area. 2. Remove oblique walls at the ports. 3. Trim the inner boundary to be flat. 4. Remove eyelets to get more reservoir volume.
V14t02		1. Add cyan inner and outer boundaries with 50-micron offset for additional black final cut. 2. Add a yellow line for additional final vertical cut.
V15t07		1. Add a horizontal eyelet at the lasso protection wall. 2. Round the entrance of the guiding gap.
V16t06		1. Two guiding walls on the inner part to restrict the outer sheath only go into that area, making the needle to obliquely inserting into the CDR.

Table 2.1 (continued)

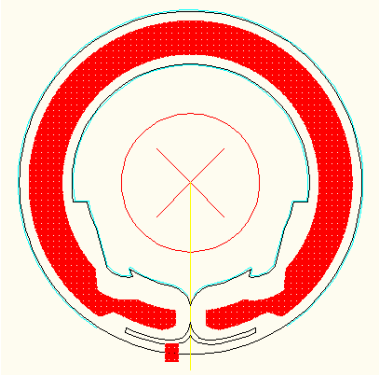
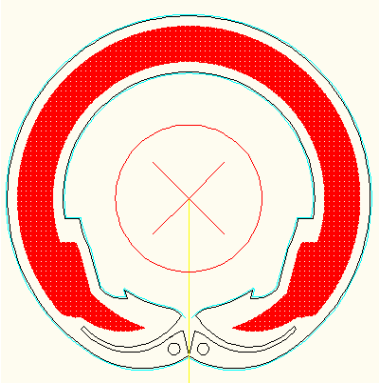
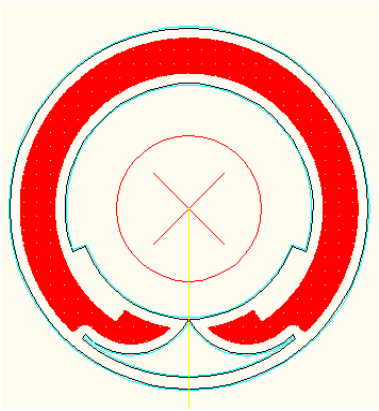
CDR ID	Figure	Design Features
V17t08		1. Recover the port thickness from 350µm to 900µm. (At least 800µm is required)
V18t12		1. Replace guiding gaps by big arc guiding gaps from V6 CDR. 2. Use the middle protrusions on the CDR as refilling ports. 3. Add two eyelets.
V19t12		1. Increase lasso guiding gaps to ease the lasso action. 2. Enlarge the port area by deploying more 800µm sidewall on the CDR to allow any rotation and any angle of injection. 3. The angle of injection is free because even the smallest area of the reservoir near the port area is 630µm.

Table 2.1 (continued)

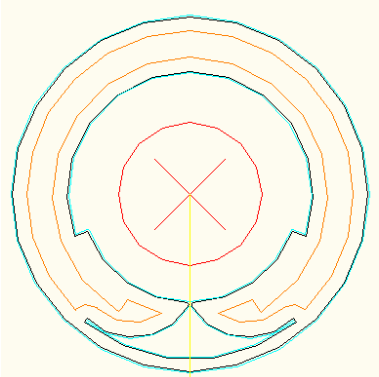
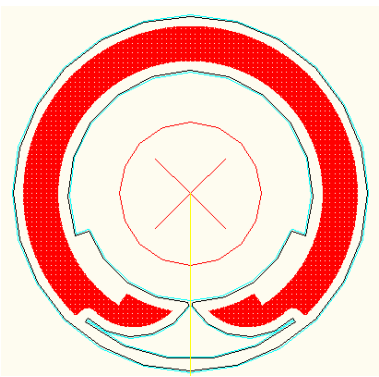
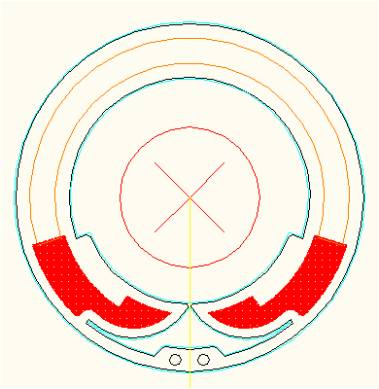
CDR ID	Figure	Design Features
V19t15 Version 1		1. Clear cut of reservoir. 2. Shrink the boundary of reservoir by 150µm in both inner and outer side to prevent cutting the sidewalls.
V19t15 Version 2		1. 3-time raster on 9 Carbothane layers to get penetration cut of the reservoir. 2. Reservoir remains the same design with 300-micron sidewalls.
V20t05 Version 1		1. Strengthen the bottom sidewall of the port area by 2-time raster. It will give a thicker bottom sidewall and therefore more support during grabbing and injection. 2. Fillet sharp corners. 3. Add two eyelets.

Table 2.1 (continued)

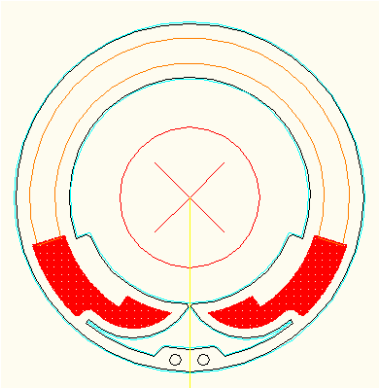
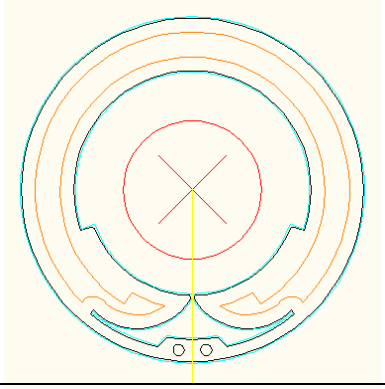
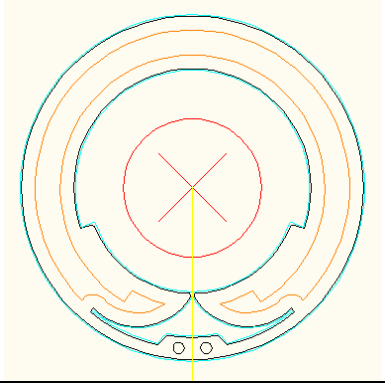
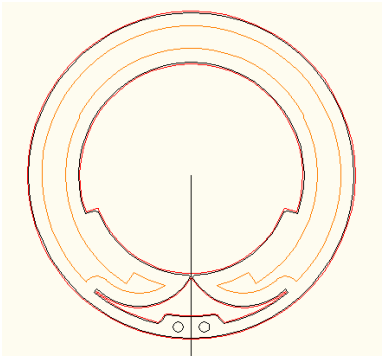
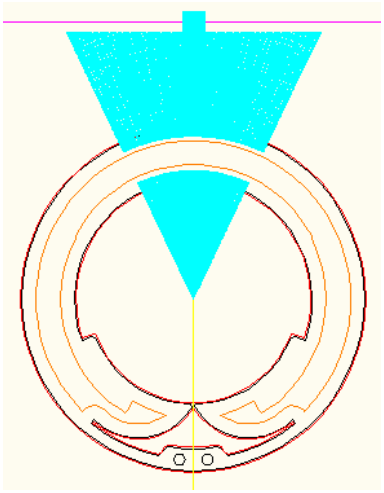
CDR ID	Figure	Design Features
V20t05 Version 2		1. Strengthen the bottom sidewall of the port area by 2-time raster. It will give a thicker bottom sidewall and therefore more support during grabbing and injection. 2. Fillet sharp corners. 3. Add two eyelets. 4. The difference between Version 1 and 2 is the sequence of reservoir peel and 2-time raster.
V21t01 Version 1		1. Use only clear cut with 450µm sidewalls. 2. Melt 9-layer Carbothane with hot plate before laser fabrication.
V21t01 Version 2		1. Use only clear cut with 450µm sidewalls. 2. Melt 10-layer Carbothane before laser fabrication.

Table 2.1 (continued)

CDR ID	Figure	Design Features
V21t02		1. Increase the sidewall near the filter area to prevent leakage from the previous testing.
V21t04		1. Embed a filter on V21t02 CDR.

Carbothane sheets at 95-100 ℃ for one minute. This will produce better sidewalls because gaps found between the Carbothane sheets are closed by the flow of the barely-molten plastic into these tight spaces. If the temperature, mechanical pressure, and heating time could be carefully controlled, it is conceivable that a more reliable product may result. Of course the ideal solution would be if the sheets could be acquired directly from the manufacturer in the desired thickness. At this time, as optimizing the manufacturing of the laminate sheets is beyond the scope of this project, all leakage of the CDR will be attributed to either the density of the laser power (green/blue on Fig 2.2) or the final cutting process.

2.3.2 Drug Reservoir Fabrication

The drug reservoir in the CDR was formed using laser ablation. Closely-spaced radially-directed, medium-power beam paths were used to ablate a drug reservoir cavity in the area scanned. The advantage of forming the drug reservoir by laser ablation is the precision and flexibility it affords. However, drawbacks are that it is a time-consuming (taking about 20 minutes for each CDR) process and that it can cause a loss of reservoir volume, because the depth of the cavity cannot be as well controlled, due to the occurrence of melting, more than ablation, with this type of laser, effectively limiting the minimum thickness of the bottom walls to 200μm. Since only a 100-μm-thick bottom is required, reservoir volume is not maximized by this method. A second pass by the laser beam may increase the depth of ablation but it also prolongs the process. Fortunately, the top wall avoids that limitation, as it is made of a single 100-μm-thick film, needing only to be laminated.

Overall, there were three laser ablation steps required to form the CDR.

Significant development time was required to optimize the method, which can be described as follows: (a) nine layers of Carbothane film are rolled flat on a glass slide, (b) they are cut all the way through by three ablation passes, (c) a top film is then added and laminated, (d) the device is carefully flipped and aligned, and (e) a bottom film is likewise laminated. Passing the beam over an area three times, instead of using higher laser power to cut through the first time, allows the localized "melting" of the plastic to partially freeze back to a solid in between passes. Notwithstanding the benefits, three passes increase the processing time of this step alone to about 30 minutes.

As an alternative to laser ablation of the drug reservoir by essentially carving it out of a thick piece of Carbothane, through cutting of the reservoir using the laser and then attachment of a top and bottom layer of Carbothane was the most commonly used method in my design, especially for later designs. Though it will expand about 130μm in the horizontal direction from the designed dimension, through cutting of the Carbothane gives smooth sidewalls and saves a lot of time. Only 30 seconds is required to achieve a through cut in three passes, and the reservoir is then peeled out by hand. The parameter of the through cut is the same as the one for cutting the CDR boundary.

2.3.3 CDR Fabrication Process

Once the separate pieces of the CDR were cut out using the laser, adhesive is applied at the filter area to attach the filter to both the bottom and top Carbothane layers. After each application of this adhesive at the desired spots (typically the inner and outer sidewalls), a Corona treatment is applied to make the Carbothane hydrophilic and to help the glue spread evenly across the surface. Then, either the filter or the eleventh Carbothane sheet is assembled, and a UV light is focused on that area for three minutes to

cure the adhesive. The filter assembly step is one of the most time-consuming in the CDR fabrication process. Attempts at simplifying this attachment process have so far been unsuccessful.

For clear-cut reservoirs using either 9 or 10 Carbothane films, two additional Carbothane films are required to form the top and the bottom of the reservoir. An alignment technique is used in this process, in which a through-cut square is centered around the yet-uncut circular outline of the eventual CDR. After the topside wall is attached to the top of the reservoir, a square outline of the incomplete CDR is carefully peeled, flipped, and placed back in the square cavity, as shown in Figure 2.4. Another Carbothane wall is then placed on the bottom of the reservoir for lamination. The square cut ensures proper alignment after flipping the CDR, for the lamination and final outline-cut passes, provided that the carrier glass slide remains undisturbed on the bed of the laser machine.

A proposed modification to the CDR to increase its volume was to generate "balloon" walls that would expand out away from the center of the CDR when drug is injected into the device. In order to form a balloon wall, a plastic piece shaped into the arc of the reservoir, and sitting over it, is pressed down, together with the Carbothane film, meant for the bottom or top wall, before lamination, creating a concave shaped top wall. The volume of drug reservoir is then able to increase due to the extra area of the wall. It is called a "balloon wall" because it would balloon once pressure is built up inside the reservoir. The advantage of this process is that the volume will become 50 μL if one wall is ballooned, and even more when both top and bottom walls are ballooned; even then, it is a challenge trying to seal the wrinkled edge of a distorted film to the sidewalls, so it is not commonly used in this work, but can be adapted to any of the proposed

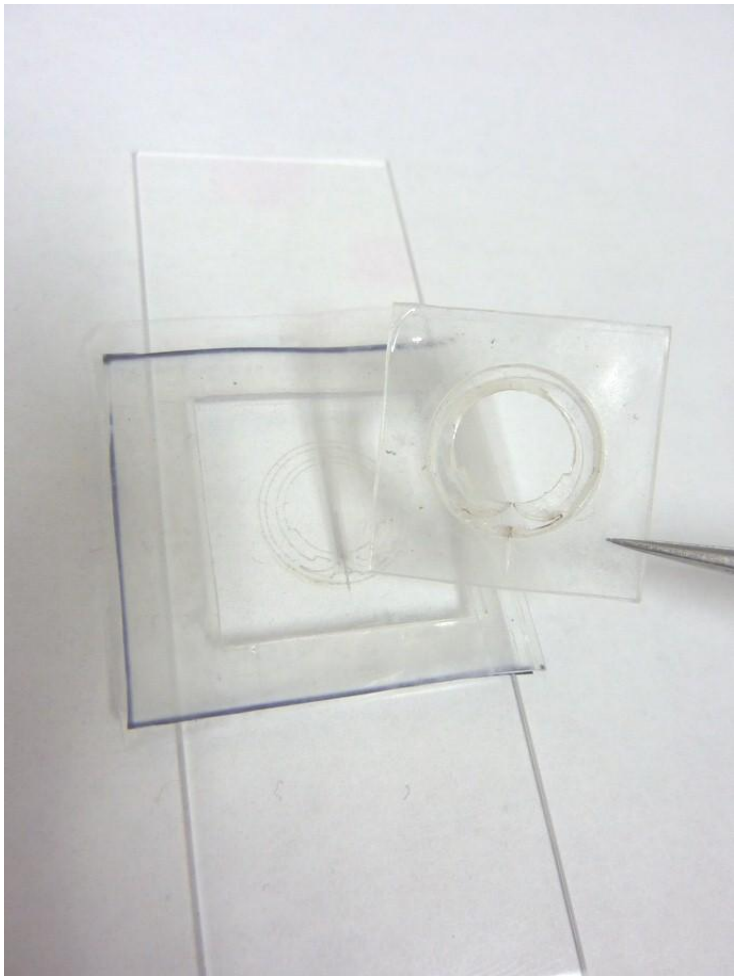


Figure 2. 4 Self-alignment mechanism

designs.

2.4 Lasso-based Designs

The basic CDR is not easily used with a lasso-based filling system, so in order to be refillable by lasso-grabbing devices, some structures had to be added to the CDR. Table 2.1 lists the evolving designs of the lasso-based CDRs. The specifications for these lasso-based CDRs include:

1. The ability to increase or keep the volume of the drug reservoir constant.
2. The ability to effectively seal both inner and outer sidewalls.

3. The ability to maintain the thickness of the refilling ports.
4. Application to CDRs both with and without a filter membrane.
5. The ability to be easily grabbed by a lasso refilling device.

Figure 2.5 shows a design of a lasso-based CDR (version 21) with a dissected view. In addition to the basic mechanisms on the original CDR, as shown in Figure 2.3, protection walls and lasso guiding gaps are added for the CDR to work with lasso-based refilling tools.

2.5 CDR Component Functions

A CDR is made from Carbothane and polyethersulfone sheets. The former forms the drug reservoirs and serves as structural material for lasso-grabbing mechanisms on the CDR. The latter serves as a membrane for releasing the drug into the lens capsule.

Carbothane is the major material for CDRs. It forms the drug reservoir's inner, outer, top and bottom sidewalls. Two injection ports are formed by thicker Carbothane inner sidewalls (800 μm) near the two ends of the ring. The extra thickness is required to ensure proper self sealing after injection. Additional structures were required to use the CDR with lasso-based injection devices. These structures essentially serve two

Figure 2. 5 Top view and dissected view of a lasso-based CDR (version: v21t02)

purposes. The first is to provide a structure that the lasso can grab on to and hold; the second is to prevent the lasso from scratching or damaging the lens capsule, which will be directly behind the CDR when it is placed in the eye. Carbothane forms the protection wall at both ends of the CDR. The channels between the protection walls and the injection valves near the end of the CDR form guiding structures for lasso loops to enter and exit the CDR easily without damaging the eye. Moreover, two eyelets are provided at the end of the protection walls so that ophthalmologists can use an IOL injector to grab the whole CDR and move it around if necessary.

A wide variety of additional structures were developed, and will be described in more detail later, to achieve a variety of necessary functions that were not necessarily clear at the outset. For version V21t04, which is the latest version for lasso-based CDRs, several structures are included to achieve a better interface between the lasso refilling devices, the CDR, the IOL and the lens capsule. A review of these features is needed to fully understand the manufacturing. These features include:

1. An inner sidewall at the filter area thicker by 150 μm to achieve better puncture-hole closure and sealing after injection.
2. An additional boundary cut (red boundary, Figure 2.6) with a 50-μm offset giving an additional final cut, and achieves a better surface finish.
3. Fillets at the port protrusion area to prevent potential sharpness of the CDR.
4. Fillets at the end of the CDR not only to prevent potential sharpness of the CDR, but also to ease the lasso loop into the lasso guiding gap.
5. Lasso guiding gaps which are designed for easy entrance of the lasso loop and reasonable fit of the drug reservoir at the port area.
6. Two eyelets located at the end of the protection walls where it is thicker than the rest

of the walls.

7. CDRs with and without a filter.
8. Flip and self-alignment which allows two additional Carbothane sheets to be attached to the reservoir.

Figure 2.6 shows the AutoCAD drawing of V21t04 CDR. The Appendix shows the fabrication features and sidewall features for each CDR.

In short, several design and fabrication features were implemented on the evolvement of the lasso-based CDRs to not only maximize the CDR drug reservoir but also ease the refilling process.

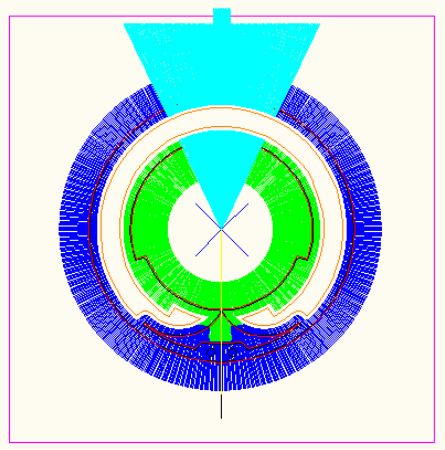


Figure 2. 6 V21t04 CDR AutoCAD design

CHAPTER 3

TESTING OF THE CAPSULAR DRUG RING

A wide variety of techniques were required to test the CDR and verify its correct manufacturing and operation. This chapter provides a description of these techniques and how they were developed.

3.1 Visual Inspection

CDR testing begins with visual inspection. Visual inspection is performed on the following:

1. Trapped air in multilayered Carbothane walls.
2. The alignment of the filter.
3. Other gaping defects on the CDR.
4. Burn marks on the CDR.

Air can be trapped in between Carbothane sheets during the stacking of either 9 or 10 layers on a 1-mm-thick glass slide. In order to avoid bubbles when stacking films, careful placement by rolling is necessary to minimize the amount of trapped air. If a bubble appears, it is necessary to start over with a new film.

Visual inspection must also be carried out to determine how well the filter is aligned to the CDR cavity. The alignment cross-hairs at the center of Figure 2.2 should be aligned with the point of the arrow-shaped filter. Another pair of cross-hairs, located on the eleventh Carbothane film, which has a precut “diffusion hole,” as shown in Figure

3.1, is used to align this eleventh Carbothane layer on the filter.

Openings in the layered walls are the most common types of defects on CDRs. If the laser power is too high or the laser machining time is too long, focusing on particular spots will burn or destroy the CDR. A reservoir built with the through-cut method that has a sidewall less than 450 μm will normally suffer damage on the sidewall as well. Carbon dust left behind by the ablated Carbothane is found mostly near the edges of the filter area. The material moving in and out of the laser-beam focal area, due to uneven surface topography, is one of the main causes of leftover carbon dust, or the inability to remove it sufficiently. On the other hand, char sometimes occurs at the boundary if the power of the final cut is too high. What's more, film-layer separation can occur because (a) the design is premature or (b) the wall layers tend to slide apart during the flipping process when using alignment technique.

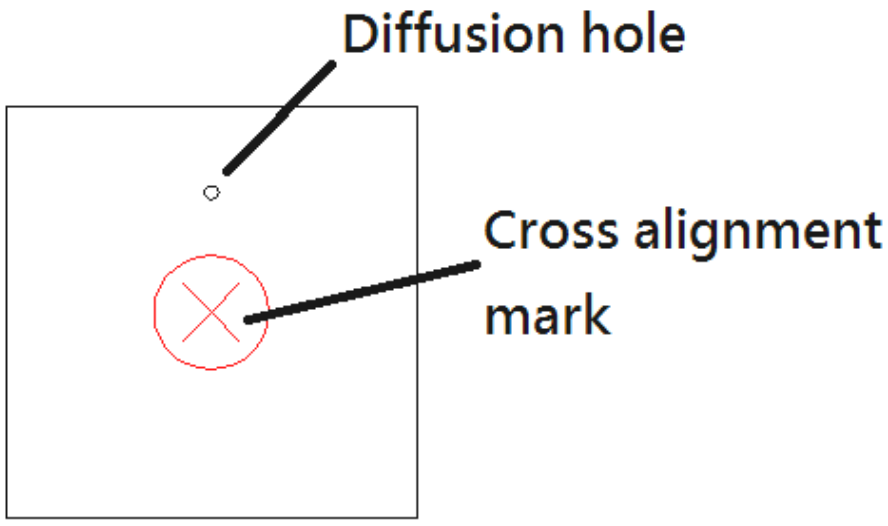


Figure 3. 1 Drawing of the eleventh Carbothane sheet with diffusion hole and cross alignment mark

3.2 Leak Testing

Leak testing was a critical step in evaluating every design. Before starting the discussion of leak testing, when using the term "opening" I mean obvious gap in the sidewalls, and by "leakage" a less severe hole which allows liquid to slowly leak from it under the pressure of fluid injection. Typically, an opening is plain to see, whereas leaks are found only by testing under pressure.

If no opening was found during visual inspection, a leak test was then performed on the CDR. Figure 3.2 shows CDRs during the leak-testing. In this test, a green-colored liquid was injected into the reservoir from the lasso-guiding gap to see how well the CDR reservoir was sealed. Often, this test was performed under an optical microscope to be able pinpoint the source of any leak.

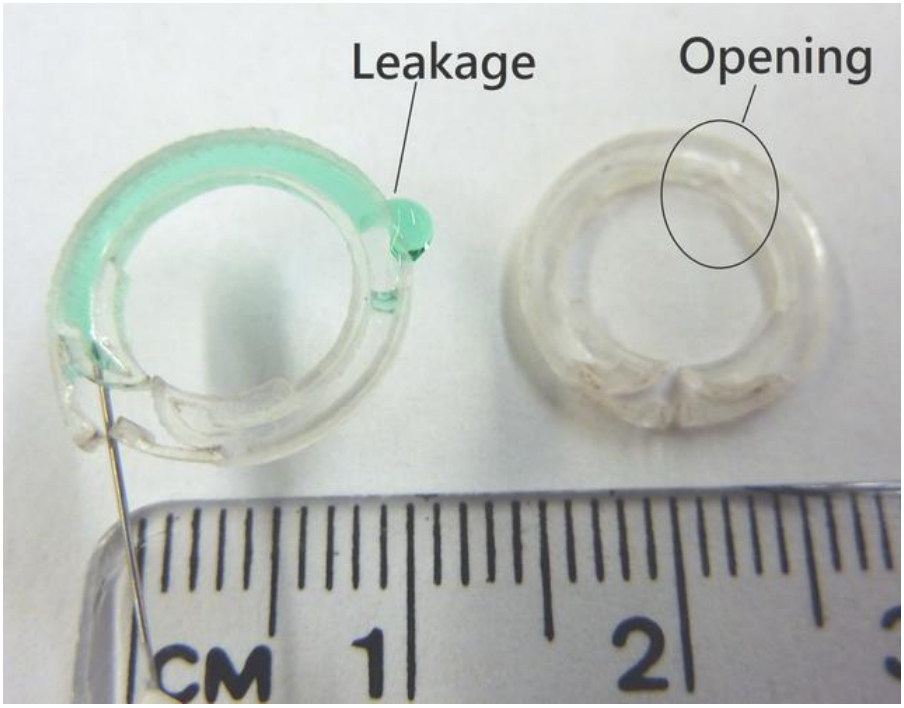


Figure 3. 2 Leakage and opening of V21t02 CDRs

Openings will occur when a region of sidewalls is damaged due to either the sliding apart of the wall layers, or because of poor design such as a dimension that was too small; rarely, it can result from trapped air in the film layers, as those in Figure 3.3. The opening in the second CDR of Figure 3.2 was caused by the layers sliding apart, which occurred during the flipping process.

Many factors can cause the CDR to leak. These factors are:

1. A minor misalignment.
2. The wrong parameters for the laser power or the laser machining time.
3. Defects in Carbothane film.
4. Inappropriate design, i.e., the sidewall is too thin or the gap between lamination and the reservoir is too small. (For most of the cases, the gap is 50μm.)
5. Lack of focus due to either the wrong Z-height (the distance between the focal point of laser beam and the honeycomb workpiece support table) settings or the clouding of the laser output lens by ejected debris.

If the leakage persists, then a different approach, or "design," is tried. The Appendix shows a classification of designs and their leakage/opening status as well as reservoir volume. Figure 3.4 shows a corresponding figure for terminology in the Appendix.

3.3 Volume Testing

The reservoir volume of the original CDR was about 20 μL: which was less than desired (optimal would be 100 μL). The Appendix shows the evolution of reservoir volume in lasso-based CDRs. In the last two models, the reservoir volume of 30 μL was achieved.

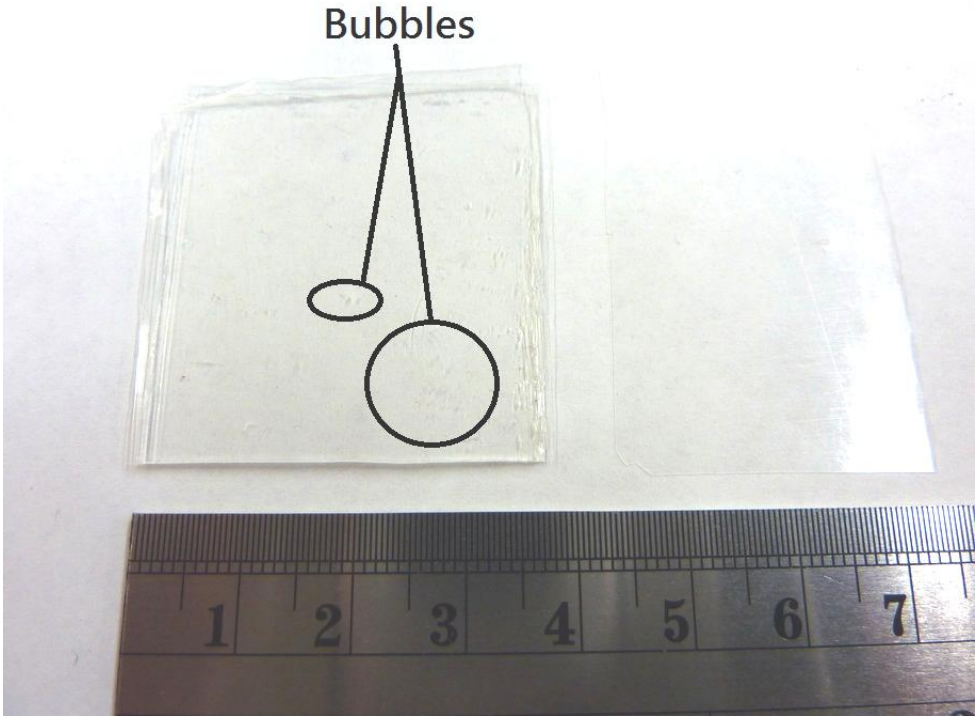


Figure 3. 3 Comparison of Carbothane sheets
(Left) bubbles in 10 layers of Carbothane sheets.
(Right) A single layer of a Carbothane sheet.

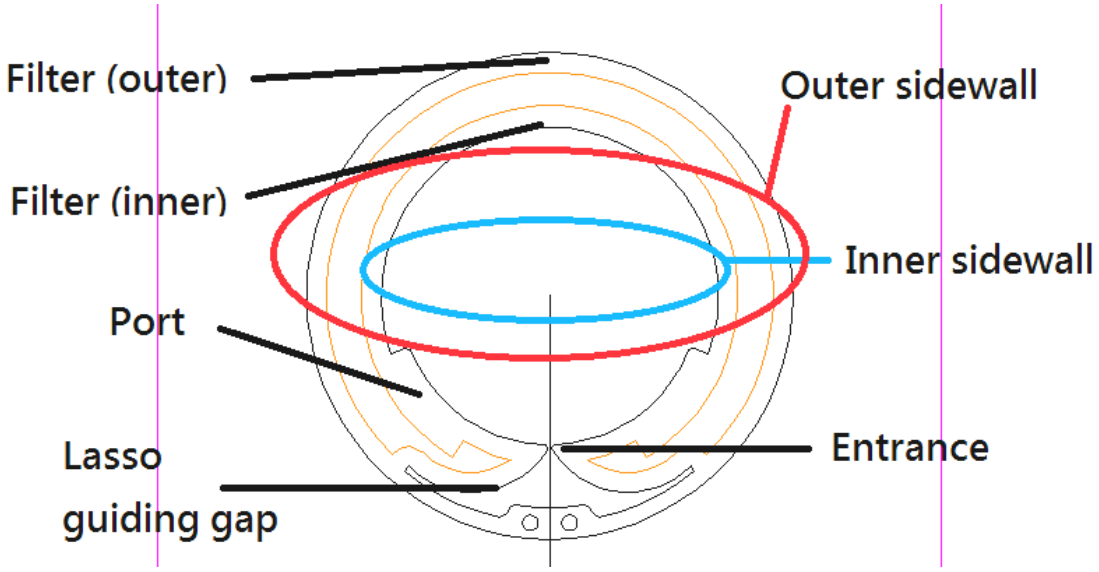


Figure 3. 4 Terminology of CDR structure for the leakage data in the Appendix

For V21t01 Version 2 as shown in Figure 3.5, the outer and inner sidewalls are both 450µm, which was found to provide the best balance between being leakproof, having good mechanical stability, and having a large reservoir volume. The volume of this version's CDR is 27 µL. Even then, the production process yield of leakproof devices was only 40%. The reason for this was not design shortcomings alone, but also misalignment during the fabrication process. A new design that provided better alignment was tried to improve yield: the V21t02 CDRs.

The V21t02 CDR, as shown in Figure 3.5, has a thicker inner sidewall at the filter area. The inner sidewall of that area is 500µm and the rest of the inner sidewall remains at 450µm. Though increasing the thickness of the inner sidewalls should have decreased the drug reservoir volume, it not only improved the yield of leakproof devices from 40% to 60%, but also increased the reservoir volume from 27 µL to 32 µL. The reason for this can be attributed to the difference in dimension of the actual-fabricated CDR and the CDR design. It will be given further discussion in Section 3.6.

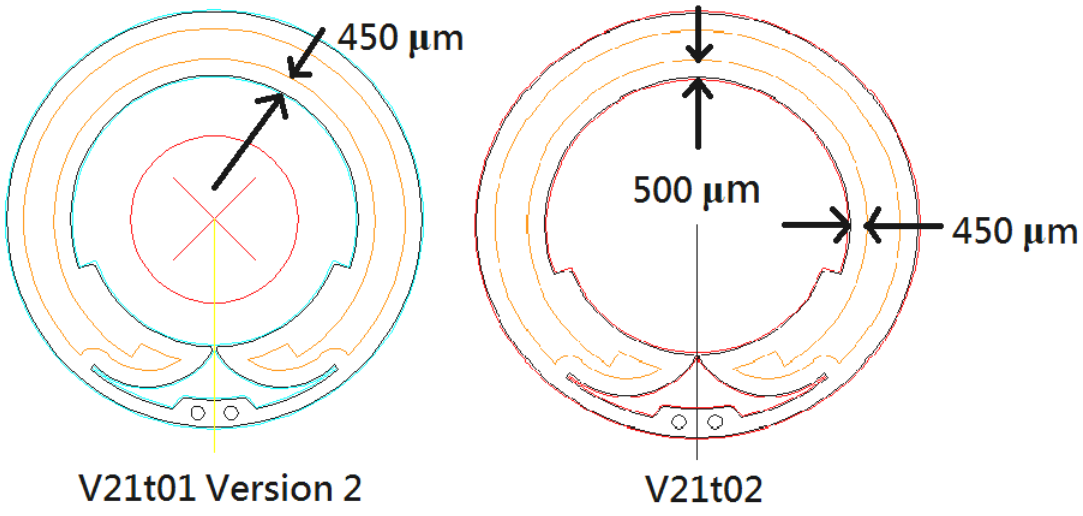


Figure 3. 5 Comparison of V21t01 Version 2 CDR with V21t02 CDR

The only difference in design between V21t02 and V21t04 is that there is a filter insertion process in the latter. The reservoir volume of the V21t04 CDR is 31 μL. Figure 3.6 shows real V21t01 Version 2, V21t02 and V21t04 CDRs.

3.4 Port Testing

In the beginning, there are four "ports" or potential injection locations on one CDR, as shown in Figure 3.7. Ports A and B are used to inject Avastin in the drug reservoir during the implantation surgery. Ports C and D are used to refill every six months to one year. It was found that the thickness of the port area needs to be at least 400 μm for it to be able to close after needle punctures well.

For lasso-based CDRs, the thickness of the port remains at 650 to 950 microns for most of the versions. The Appendix shows the thickness of each design. Since the outer and inner diameters of a CDR are fixed to be 12.4mm and 7.6~8.6mm, respectively, there needs to be a delicate balance between the volume of the drug reservoir and that taken up by the port thickness. Thinner ports afford the injection needle

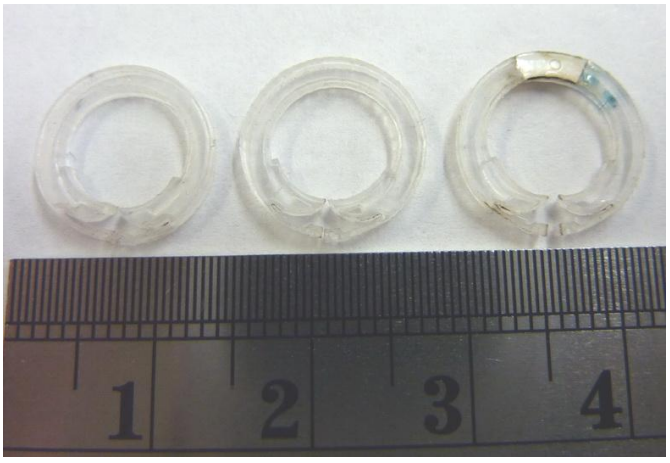


Figure 3. 6 Different V21 CDRs
(From left to right) V21t01 Version2, V21t02 and V21t04 CDRs

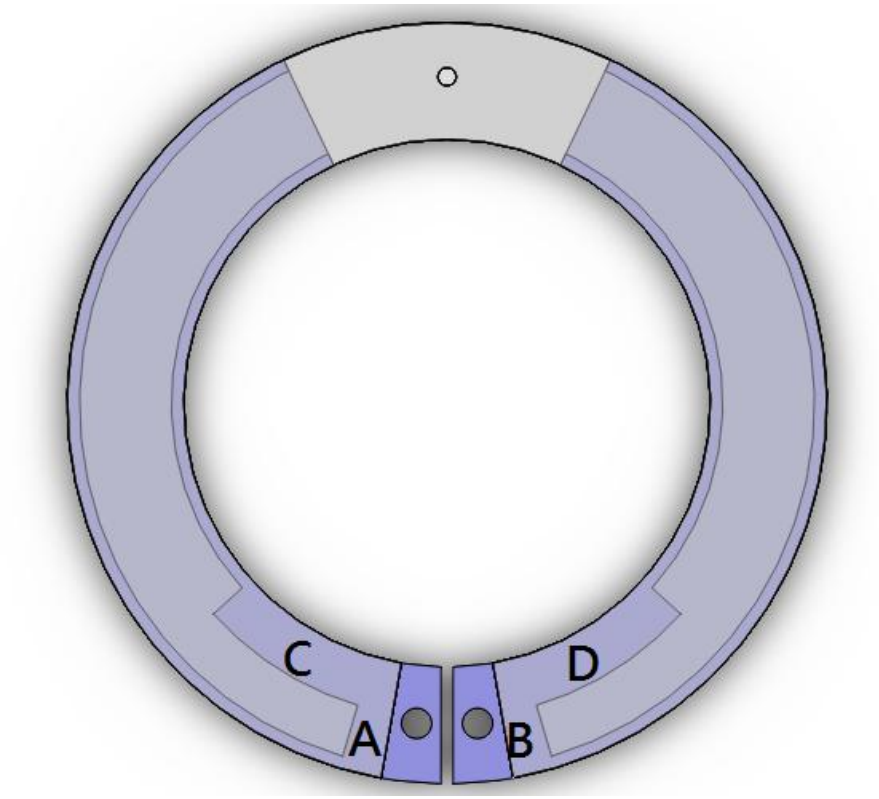


Figure 3. 7 Ports in the initial CDR

more room to maneuver because the reservoir below the port is deeper. Figure 3.8 shows a detailed view of the progress of injection with a needle penetrating the port and reaching the drug reservoir. On the other hand, ports with thickness less than 400μm have a chance to become leaky once punctured.

In Figure 3.8, the progress of needle penetration into the CDR is divided into seven illustrative steps or needle locations. In location 1, a 30G needle is ready to penetrate the port. In location 2, the tip of the needle punctures the port area. It will leak if the operator applies the drug during this step since the needle orifice is still exposed to just outside the CDR in the lens capsule. In location 3, the orifice of the needle is embedded in the port area. In location 4, a part of the orifice reaches the drug reservoir. The operator can refill the drug reservoir during this step. In location 5, the entire orifice of

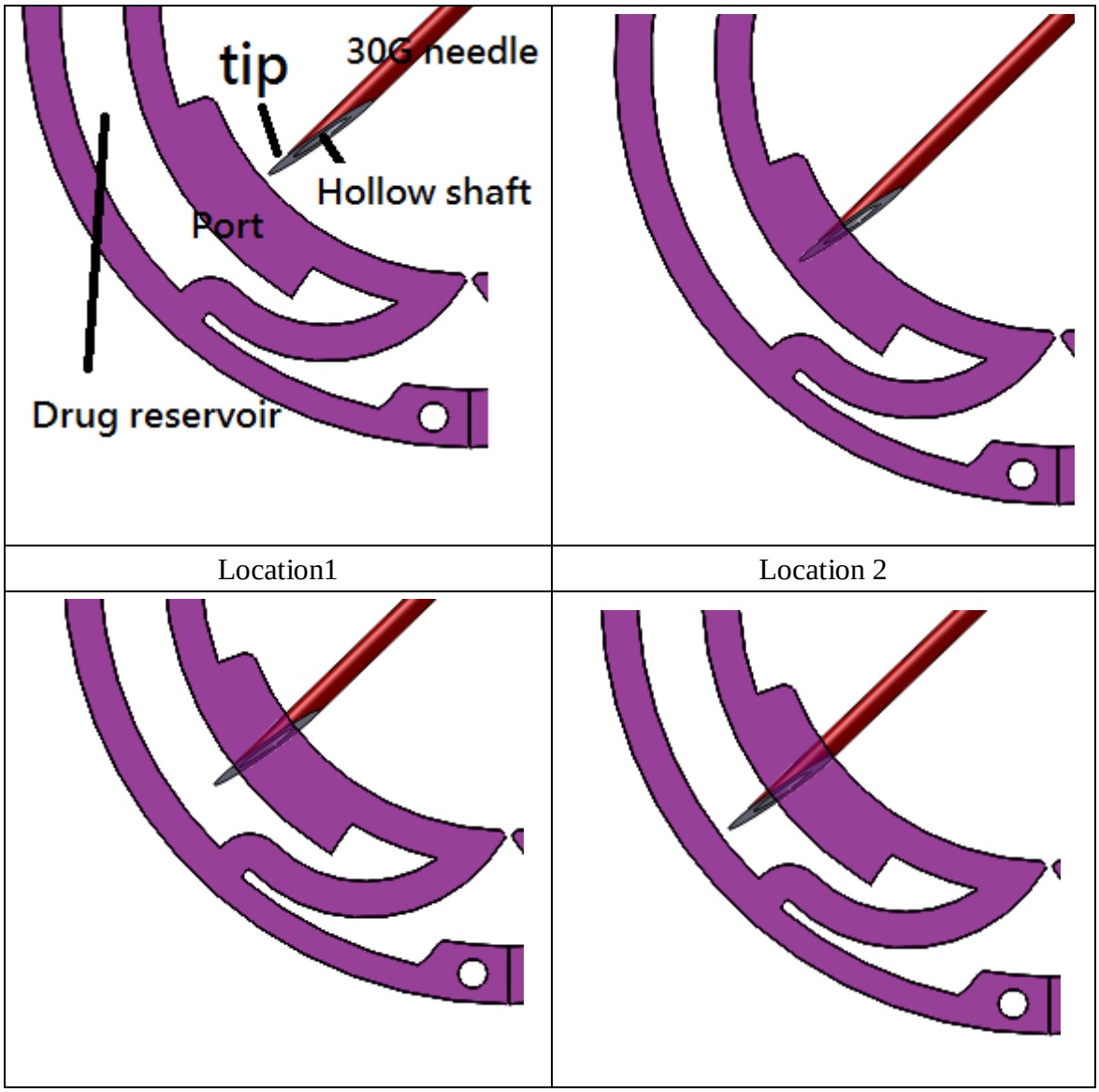


Figure 3.8 Injection process of a 30G needle and a v21 CDR
Note that the lasso loop and the top and the bottom Carbothane walls are not shown in this figure.

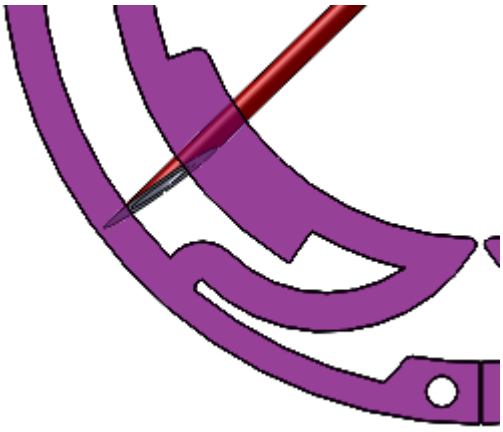
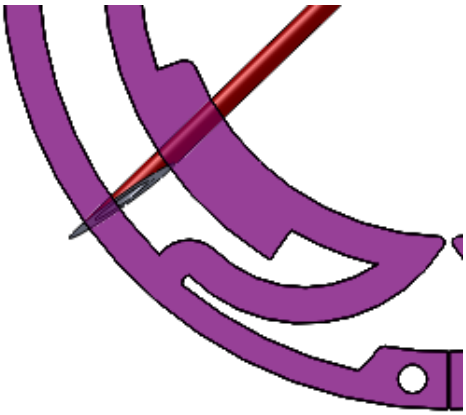
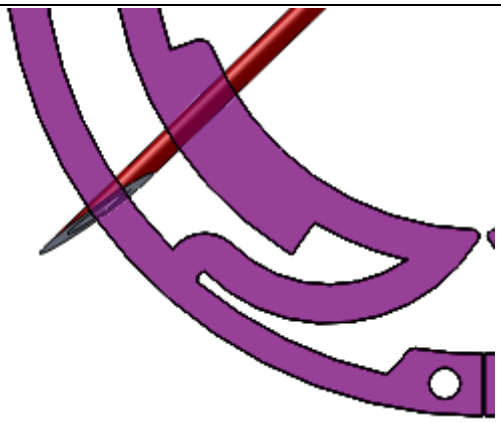
Location 3	Location 4
	
Location 5	Location 6
	
Location 7	

Figure 3. 8 (continued)

the needle is in the drug reservoir while the tip of the needle stabs the outer sidewall of the CDR without penetrating it. The operator can also refill the drug reservoir in this location. As long as the tip does not penetrate the outer sidewall, there will be no leakage. In locations 6 and 7, since the tip penetrates the outer wall, the drug will be released into the lens capsule, and will cause a leakage. In short, locations 4 and step 5 are the only permitted locations during which operators can refill the drug reservoir. As it is difficult to ensure that the operator of the injection syringe is in these locations, the length of the locations should be as large as possible to help ensure a successful injection.

3.5 Grabbing and Refilling Test

In order for the CDR to be refilled after placement in the eye, a method for holding the CDR in place before injection is required. A lasso-based approach was chosen to grab and secure in place the CDR for injection. As noted previously, specific structures were added to the CDR to help with grabbing the CDR and securing it, as well as to protect the eye from the metal lasso. A lasso gap was also added to aid in guiding the lasso to the proper location for grabbing. Either the lasso gap or the position of the portis modified in the lasso-based CDRs from V1 to V21. The goal was to simplify the process for the operator to grab and secure the CDR. Several issues were found related to these structures. For instance, if the drug reservoir at the port area is larger, it gives more freedom for the needle to inject. However, it will decrease the size of the lasso guiding gaps, as shown in Figure 2.4, and therefore makes it more difficult for the lasso loop to grab the CDR.

Several versions of CDRs were tested to enable the simplest grabbing process for the operator. Figure 3.9 shows the progression of the designs of the lasso-based CDRs. Green arrows indicate the area and direction that an injection needle would follow.

A progression of designs based on testing the fabricated designs and modifying the design for a new iteration, as appropriate, led to the final design. In Figure 3.9, the V2t06 CDR, an early version, has a thin lasso guiding gap for the lasso loop to enter. In this version the drug reservoir is not sealed at the gap and leaks, so the sidewall is increased in the V5t08 CDR to achieve a better seal. Because the gap entrance is small, it is difficult for the lasso loop to enter the lasso guiding gap. An oblique end is introduced in the V5t08 CDR to ease the entrance process of the lasso loop. In the V11t12 CDR, another angle of injection is experimented with to achieve a relatively

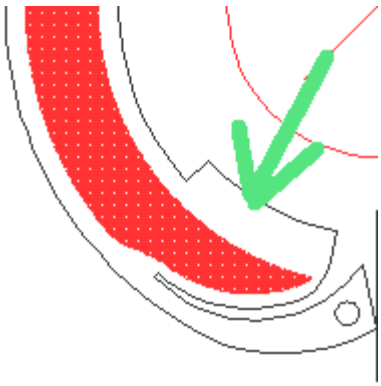
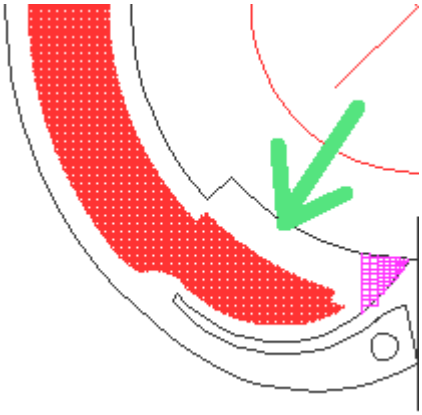
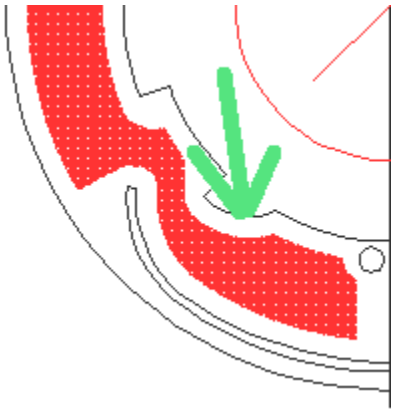
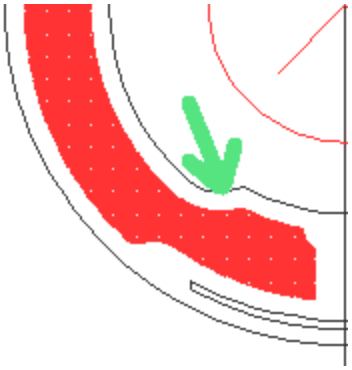
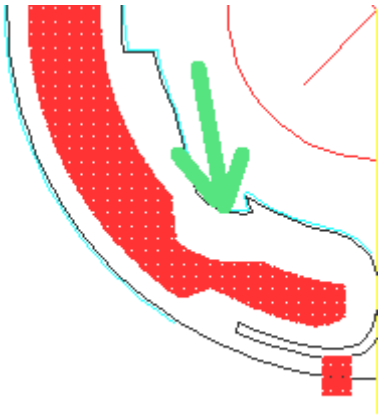
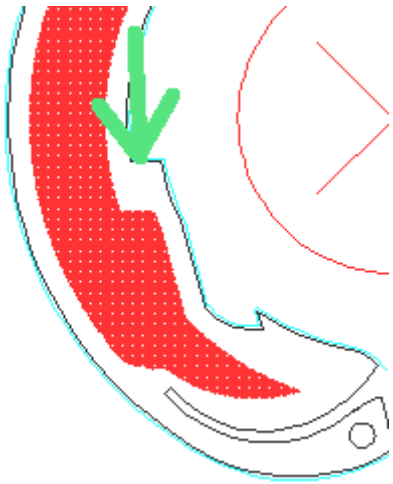
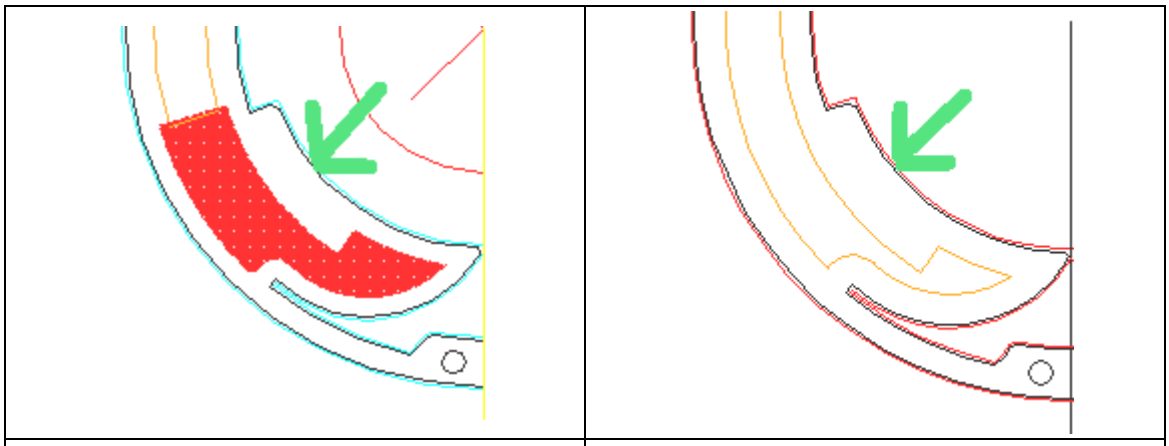
	
V2t06 CDR	V5t08 CDR
	
V11t22 CDR	V13t09 CDR
	
V17t18 CDR	V18t12 CDR

Figure 3.9 Evolution of refilling mechanisms on lasso-based CDRs



V20t05 CDR	V21t02 CDR

Figure 3. 9 (continued)

wider range for the injection needle inside the drug reservoir. Since the needle may rotate during the injection, either modification of the suspension wall for the needle or a shorter version of the lasso gap is tested. The V13t09 CDR has a shorter lasso guiding gap. Compared to the V11t22 CDR or the V12t04 CDR (shown in the Appendix), the lasso loop will stop exactly at the end of the lasso guiding gap, and therefore the needle can remain in the same position every time. The V17t18 CDR has both a shorter lasso guiding gap and needle suspension walls. The needle suspension walls on this CDR will guide and fix the outer sheath of the refilling device and thus provide a fix-angled injection. Nevertheless, the drug reservoir at the port area is small and it is difficult to inject the drug directly into it. The V18t12 CDR is introduced to solve this problem. A big drug reservoir is created by moving the port to the middle of the CDR. Though this V18t12 CDR is designed to be refilled at the center port, it turns out that the needle stabs the lower side of the CDR every time because there is no structure near the middle port to prevent the needle from going through when pulling the lasso loop to grab and fix the CDR.

For the V20t05 and the V21t02 CDRs, the lasso guiding gaps are increased to ease

the entrance process of the lasso loop. Also, the port area is increased so that injection needles at different angles can inject through the port. The V20t05 CDR has a scattered reservoir near the port area which is designed to provide more longitudinal support during an injection due to thicker top and bottom sidewalls. However, the support is limited, and therefore only a clear cut reservoir is used in the V21t02 CDR. A V21t02 CDR with dimensions is shown in Figure 3.10 in which the minimum reservoir thickness is 334.9μm and the maximum is 1123.1μm. Since the length of the orifice for a BD 30G1 needle is about 680μm, the operator can use all of the port area in the V21t02 CDR to refill. This design worked well in nearly all tests, so is chosen as the final port design.

3.6 Dimension Verification

The actual dimensions obtained in the manufactured devices were compared to the dimensions proposed in the design drawings. Many of the design dimensions were

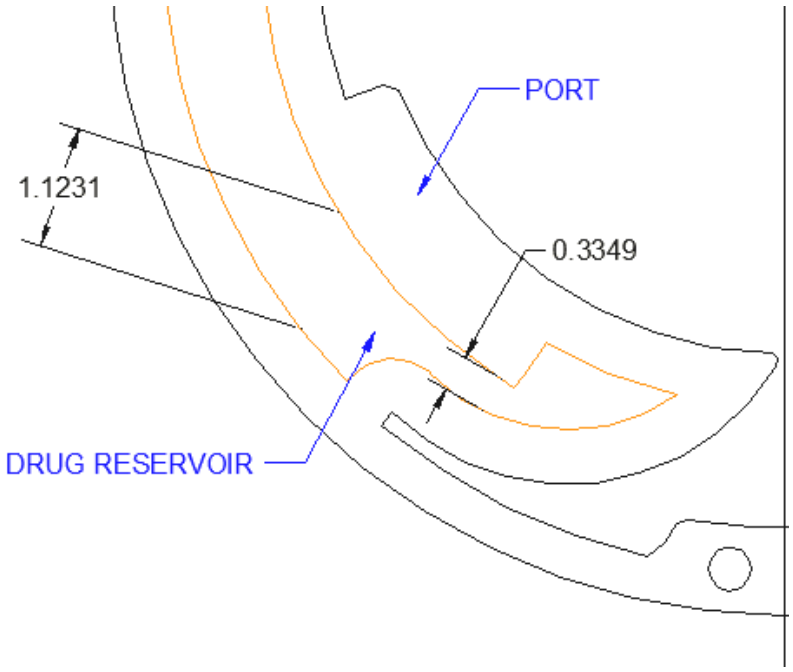


Figure 3. 10 The port area in the V21t02 CDR with dimensions

The needle orifice has sufficient space within the port area.

critical, so verification that these dimensions were fabricated correctly was needed to ensure that the appropriate conclusions were drawn. For example, a 450 μm thick port is required in order for self-sealing to occur after refilling. For the rest of the sidewalls on the CDR, it is important to achieve the desired inner and outer diameter because the CDR must remain between the tension ring and the IOL. The thickness of the sidewalls is less important once a sealed reservoir is achieved. The Appendix shows a comparison of dimensions in V21t04 CDRs.

Various factors can result in a change of dimensions from the proposed design. Sliding of the Carbothane piece during the self-alignment and flipping process is one of the main causes that led to improper fabricated dimensions, while other reasons include the movement of the honeycomb workpiece support table of the laser machine and debris on the focus lens of the laser machine. The change of dimensions leads to the change of drug reservoir volume in the series V21 CDRs, in which designs with nominal thicker sidewalls actually have a higher drug reservoir volume than some designs with thinner nominal sidewall dimensions. Thus, improper manufacturing can lead to results that are not consistent if dimensional variation is not taken into consideration.

CHAPTER 4

DESIGN OF THE LASSO AND INJECTION MECHANISMS

Once the CDR had been modified to work with a lasso-based system for securing the CDR for injection, the actual lasso tool needed to be designed. Of course, these two devices were designed in parallel, so changes to one necessitated changes to the other, or at least improved the interface between the two components. This chapter will review the design steps for the lasso-based tool for securing the CDR for quick and accurate drug infusion into the CDR.

4.1 Materials

Materials used on the lasso grabbing mechanism can be divided into two parts: the intraocular part, which will be inserted into the lens capsule during the refilling process, and thus should be biocompatible, and the external part, which will remain outside of the human body at all times, and can be made from materials that are not biocompatible.

The materials used for the intraocular part of the grabbing devices are stainless steels and nitinol wires. The former has been used in medical surgery for a long time [5-7], while the latter has been used in biomedical applications and is becoming more and more important because of its superelastic properties [8]. Stainless steel 304 is used as the main structural material for the lasso-based grabbing tool. It is composed of 76.9% iron, 0.06% carbon, 14.6% chromium, 6.9% nickel, and 1.5% manganese in weight [9]. A 30 gauge needle is used as an injection needle for the lasso-based grabbing tool. It is

made of stainless steel and sterilized in advance. Nitinol wires (Model: Flexinol Actuator Wire 70C series) with diameter ranges from 50.8 to 177.8 μm are used in the intraocular part as well.

For the external holding part, a plastic knob and tape is used currently, to hold and actuate the device, but they will be replaced with an automatic actuator in the future with two actuation buttons corresponding to grabbing and injection, respectively. Piezoelectric actuators have been shown to be more suitable for medical applications than traditional motors because they do not generate a magnetic field, so piezoelectrics will likely be used to drive the fully automated tool.

4.2 Design of the Lasso Devices

Different shapes of lasso loops are designed to not only ease the grabbing process but also achieve a secure attachment between the refilling device and the lasso-based CDRs. Figure 4.1 shows a drawing of a lasso-based grabbing tool. The lasso-based grabbing tool consists of an outer sheath, a lasso loop and an injection needle. The outer sheath is a 2 cm long 23 gauge stainless steel tube. The inner and outer diameters of the tube are 508 μm and 635 μm, respectively. The injection needle is a 30 gauge needle (Model: BD 30G1 PrecisionGlide Needle) which is 312 μm in diameter and 2.54 cm (one inch) long stainless steel needle. Figure 4.2 shows a cross-sectional view of the needle inside the outer sheath. Since the actual sidewall of the outer sheath is smaller than it states on the website [10], a nitinol wire thinner than 152.4 μm (0.006 inch) in diameter can be used as the lasso loop. Thicker lasso loops can provide additional support when they go into the lasso guiding gap in attempts to reach the end of the gap, therefore easing the grabbing process. In this article, lasso loops ranging from 50.8 μm to 177.8 μm

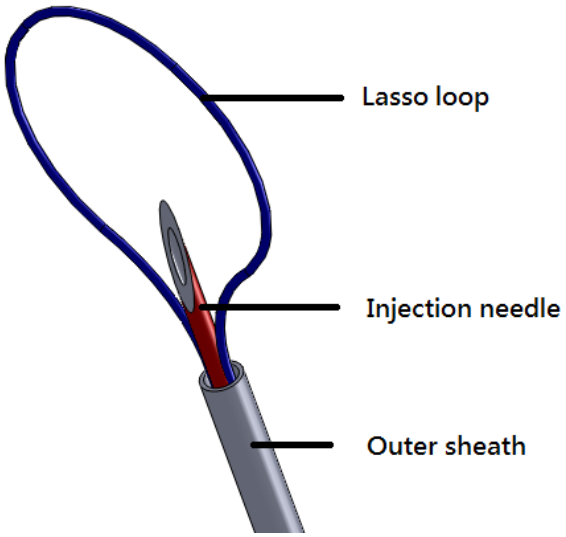


Figure 4. 1 Drawing of a lasso grabbing device (version 6)

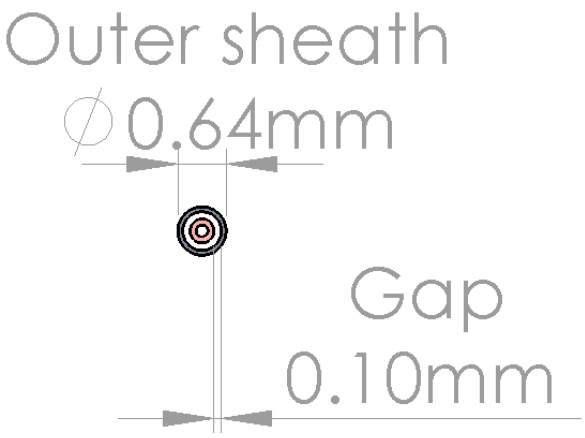


Figure 4. 2 Cross-sectional view of the gap between the outer sheath and the injection needle

(0.002 to 0.007 inches) are tested.

A lasso loop made with either stainless steel or nitinol is bent to become an arc shape to grab the CDR via the lasso guiding gap. Lasso device V1 consists of a 20mm long 23 gauge stainless steel tube as the outer sheath, a 2.54 cm long 30 gauge needle as the injection needle, and three 50.8 micron diameter nitinol wires as the lasso loops in Figure 4.1. Lasso device V2 consists of the same materials as the ones in V1, but longer nitinol wires are used to ease the taping process. Lasso device V3 consists of a 20 mm long 23 gauge stainless steel tube, a 2.54 cm long 30 gauge needle and one 127 micron diameter nitinol wire. The needle is ground to reach a 292.1 micron outer diameter in order to fit into the stainless steel outer sheath. Lasso device V4 consists of a 152.4 micron diameter nitinol wire instead of a 127 micron one in V3, as it is difficult for the needle to go in the outer sheath because the lasso loop is too thick. Figure 4.3 shows lasso devices from V1 to V4.

One of the challenges that came up during manufacturing was how to cut the steel tube without a variety of tools for dealing with this challenge at larger scales; this was not a simple problem. Wire cutters were used initially, but they left sharp edges and deformed the steel tubing. A Dremel tool with a cutting wheel was used instead of a wire stripper and a diamond-coated grinding bit was used to clean up any edges. Figure 4.4 shows the difference at the cutting end using the two methods. The Dremel tool not only provided a smooth cutting surface, but also maintained the shape of the tube. In other words, the tube remained a round shape after cutting; therefore, a larger space inside the tube is available and thicker nitinol wires can be applied in the same outer sheath. These well-cut 23 gauge stainless steel tubes are used as outer sheathes beginning from Lasso device V5.

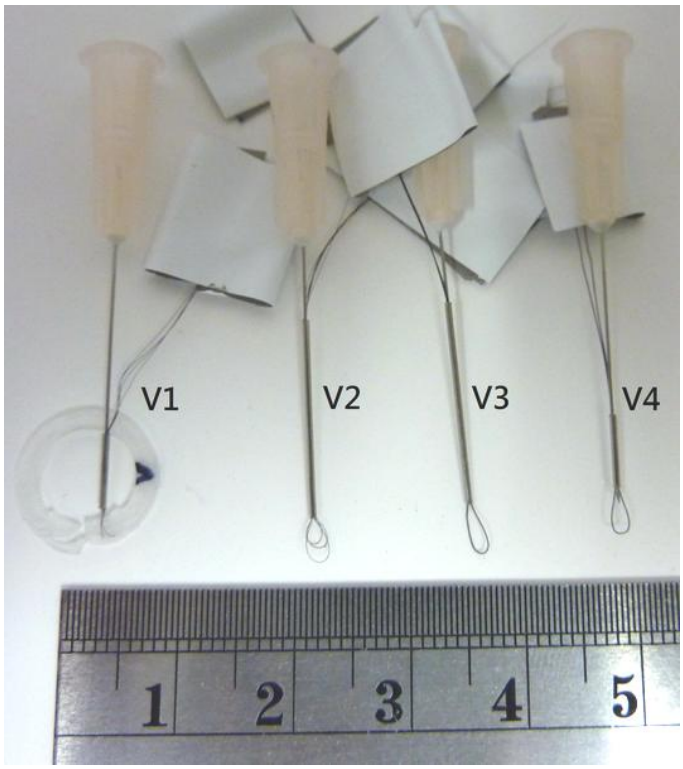


Figure 4. 3 Lasso devices V1, V2, V3 and V4

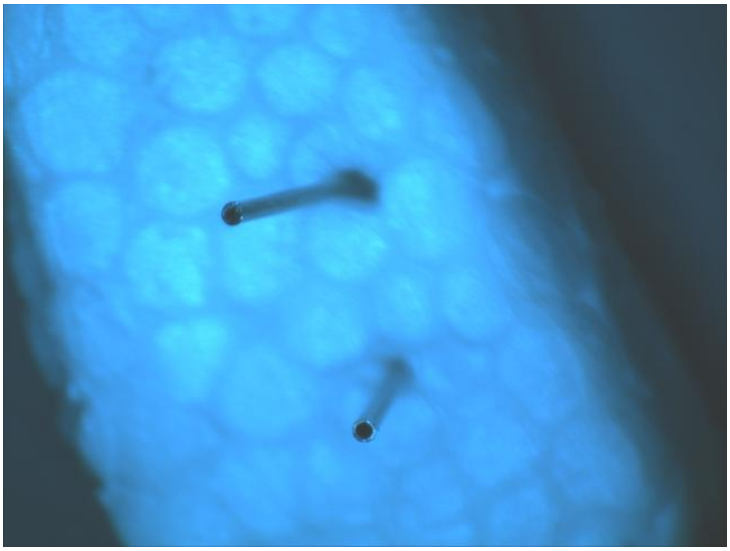


Figure 4. 4 Cut edge of the 23 gauge stainless steel tube
(Top) Cut using a wire stripper and then polished using a diamond-coating grinding.
(Bottom) Cut using a Dremel tool with a cutting wheel.

Lasso device V5 consists of a 23 gauge stainless steel outer sheath, a 127 μm diameter nitinol wire and a 30 gauge needle. The nitinol wire is heated on a hot plate for 2 minutes at 100℃ in order to increase the ability of the wire to recover its initial shape after refilling. However, the results showed that the process is useless and unnecessary. Lasso device V6 consists of a thicker nitinol wire, which is 177.8 μm in diameter. The needle is ground to be able to fit in the outer sheath. Though the thicker nitinol wire can ease the grabbing process, it is difficult for it to inject because the tolerance between the needle and the outer sheath is near zero, as it has to be pushed overly hard in order to move the needle. Figure 4.5 shows lasso devices V5 and V6.

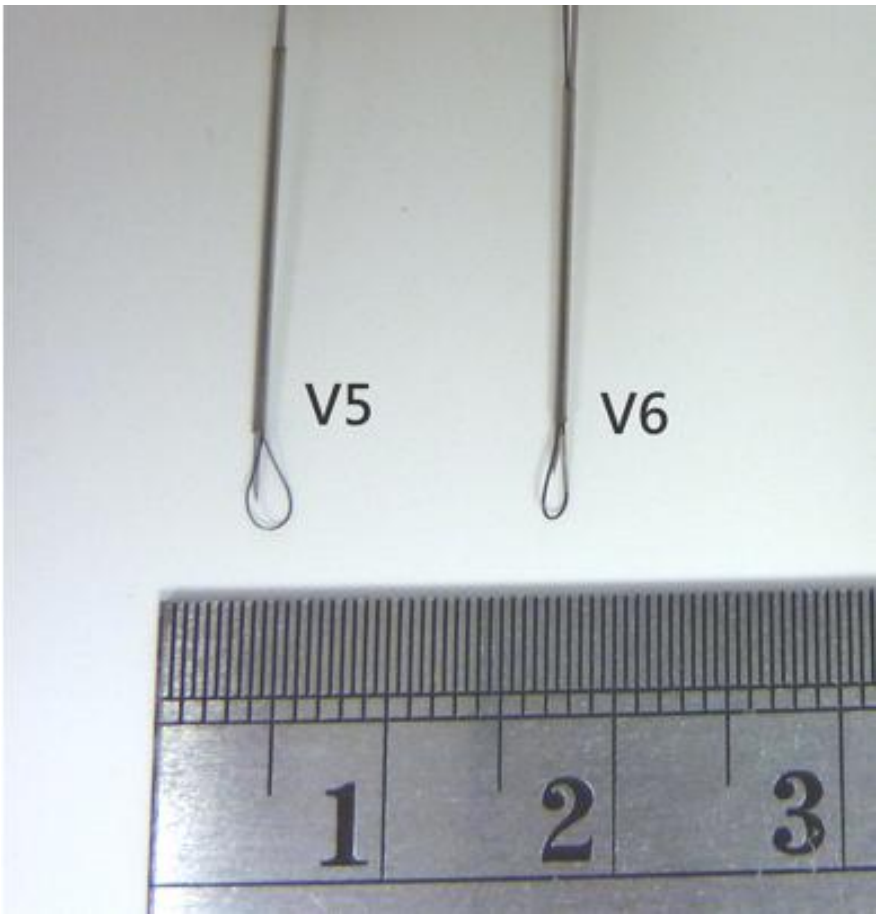


Figure 4. 5 Lasso devices V5 and V6

Additional fabrication processes are applied to the nitinol wire on the V7 and V8 versions of the lasso-based injection tool. A mold is used to make the lasso wire into the desired loop shape. Figure 4.6 shows a series of mold designs and Figure 4.7 shows a series of Teflon molds. Figure 4.8 shows lasso devices V7 and V8 series. Because nitinol wire will expand after molding and pressing, the mold has to be made smaller in size than eventually needed in order to achieve the desired shape of the nitinol loop. Lasso device V8.4 introduces an extra freezing process to let the temperature of the lasso loop drop down to -20℃ for 100 minutes. However, this tempering process fails on nitinol because the nitinol still very soft and will lose its original shape after the refilling process.

Lasso device V8.5 includes the same outer sheath and the injection needle as the V8 series, but the lasso loop is not covered with Carbothane and therefore no heat treatment is required. The nitinol wire is pressed by the V5 mold and forms the lasso shape. Lasso device V8.6 is almost the same as V8.5, but the lasso loop is formed by the V8 mold.

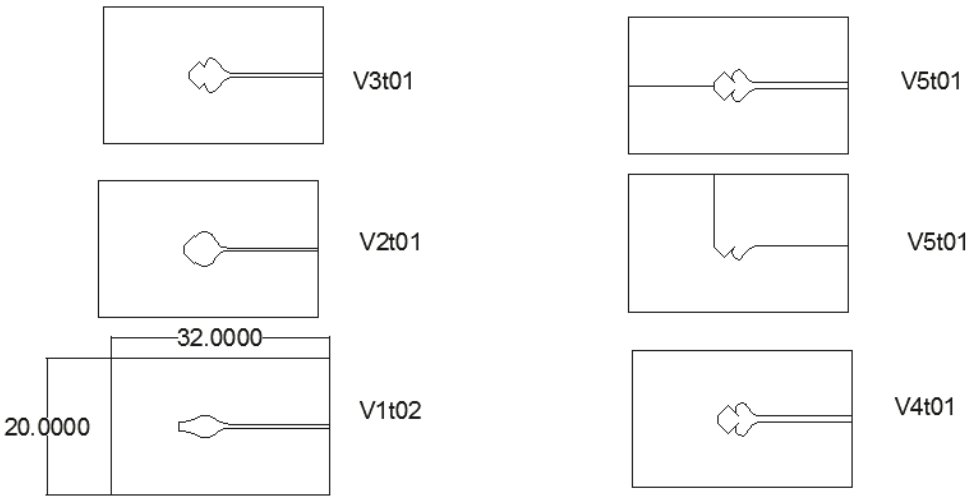


Figure 4. 6 Designs of molds for lasso loop

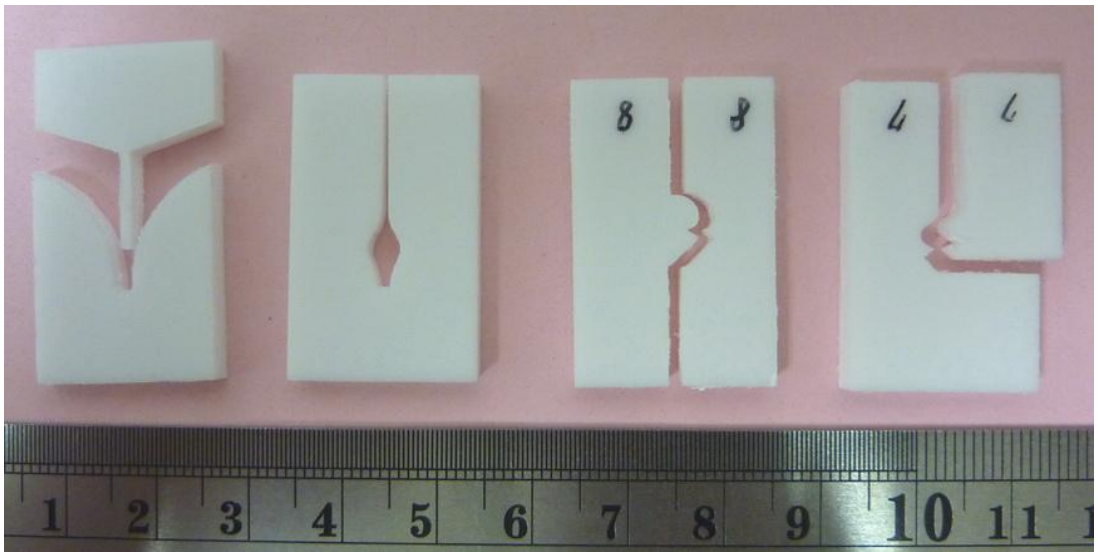


Figure 4. 7 Teflon molds for lasso loop

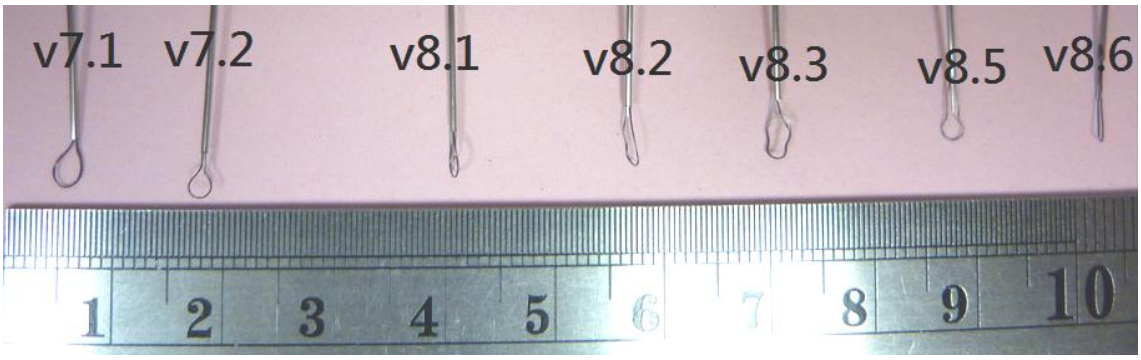


Figure 4. 8 Lasso device V7 and V8 series

Lasso device V9.1 is designed with a free-end lasso loop in which only one end of the nitinol wire is fixed while the other remains free. When pulling the lasso loop into the outer sheath, it can rotate the CDR and establish a 90 degree contact between the CDR and the grabbing device.

Several approaches are proposed and tested during the design of grabbing and injection mechanisms. Cut using a Dremel tool with a cutting wheel gives a smoother cutting end of the stainless steel tube and thus a wider nitinol wire can be assembled into the same tube. Additionally, several materials and processes are implemented on the nitinol loop to achieve a self-recovery feature.

CHAPTER 5

TESTING THE LASSO-BASED GRABBING TOOLS

Once the CDR and the lasso-based grabbing and injection tool had been developed, full testing of both components was completed. The various functions of the devices were analyzed and characterized.

5.1 Lasso Refilling Procedure

The refilling process using the lasso-based injection tool can be divided into six steps, as shown in Figure 5.1 [11].

Since the CDR is placed into the lens capsule from a 3 mm incision at the edge of the cornea, the same incision is used to fill the CDR with Avastin during the implantation surgery (if not already done). Figure 5.2 shows a schematic diagram of the refilling process. A similar 3 mm incision is made and used to refill Avastin in the CDR when refilling is required.

5.2 Test of Lasso-Based Injection Tools

Testing of the lasso-based injection tool takes place in a 13.5 mm diameter glass vial with water to simulate the free-floating situation in the lens capsule. A CDR filled with water is placed on top of the water in the glass vial, and a lasso device is used to grab and refill the CDR, as shown in Figure 5.3.

Several versions of lasso devices are designed and tested to achieve an easier interface for the operator to grab and refill the free-floating CDR. The design aspect of

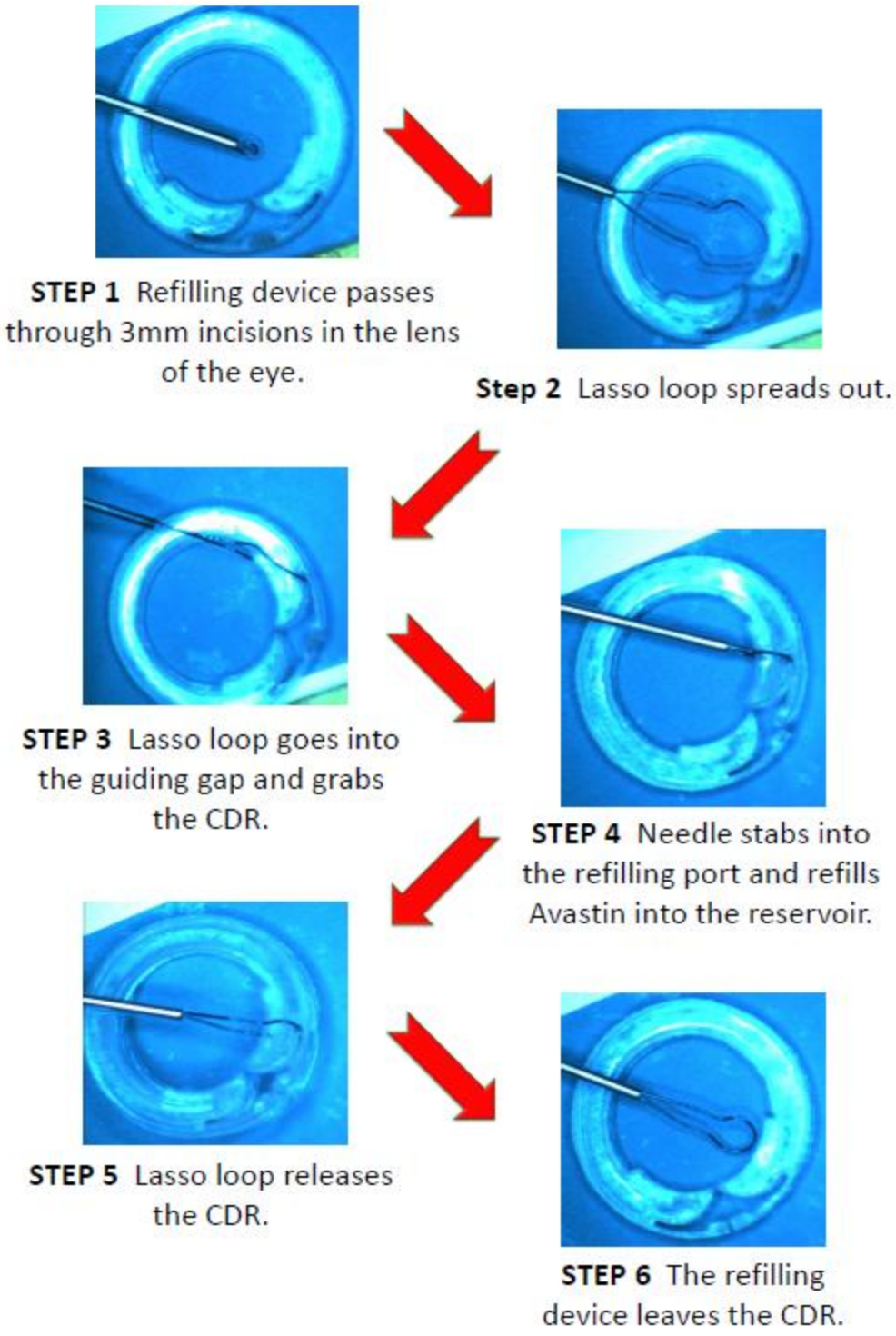


Figure 5. 1 Refilling procedure of the lasso device [11]

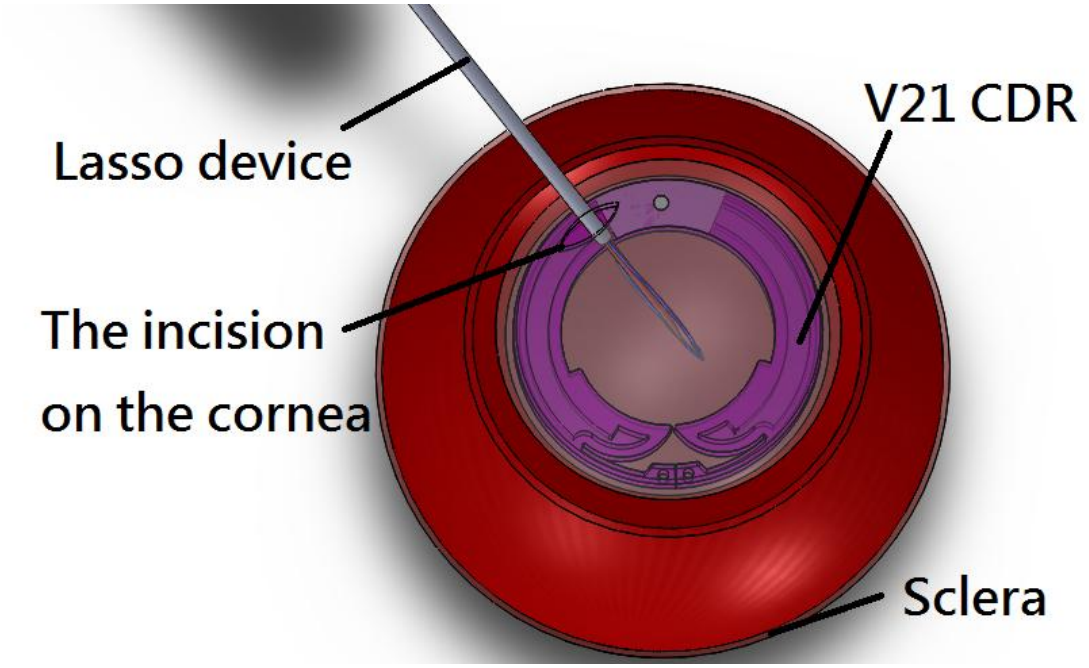


Figure 5. 2 Schematic diagram of the refilling process
A lasso device passes through the 3 mm incision on the cornea to grab and refill the V21 CDR. (The iris is hidden to show the detail inside the cornea.)

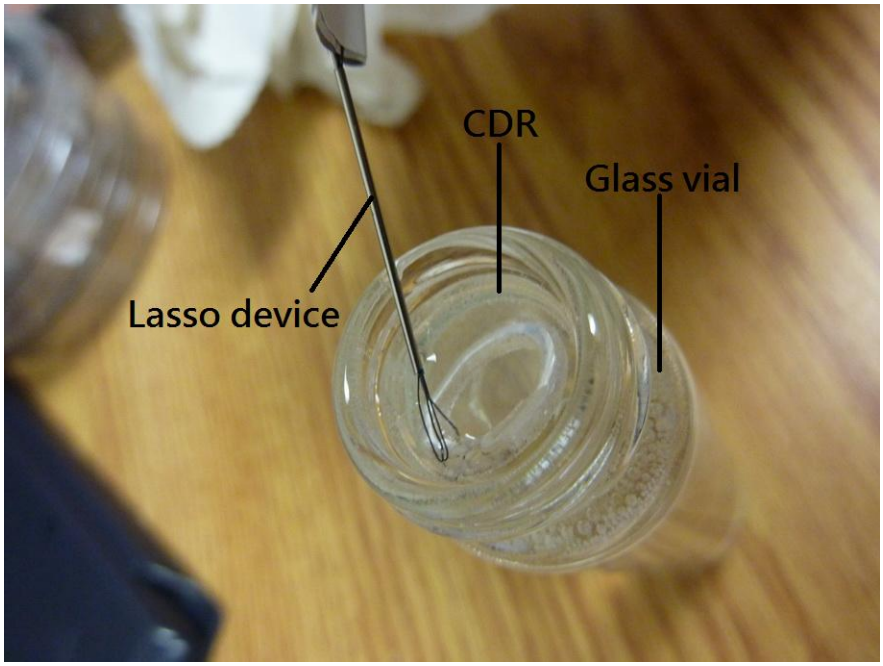


Figure 5. 3 Test of a lasso device to grab and refill a CDR in a glass vial

each version of lasso-based injection tool was described in Section 4.3 previously.

Lasso device V1 uses three 50.8 μm (0.002 inch) diameter 70 mm long nitinol wires as lasso loops. Because the nitinol wires are too short, it is difficult to operate. Lasso loops are lengthened in the lasso device V2 in which a 110 mm long nitinol wire is used for the lasso loops. Three loops give multiple contact joints between the loop and the CDR port, therefore lowering the possibility of CDR rotation during injection. However, these 50.8 μm diameter nitinol wires are too soft and it is difficult for the lasso loop to go into the lasso guiding gap. Lasso device V3 is proposed to use only one 127 μm (0.005 inch) diameter nitinol wire as the lasso loop. In this version a 30 gauge needle is ground to a thinner diameter to prevent from blocking in the outer sheath. Experiments show that this V3 device can enter the lasso guiding gap and grab the CDR relatively easily, but the CDR will rotate when injecting the needle into the port. Lasso device V4 has a 152.4 μm diameter nitinol wire as the lasso loop. Though the needle is ground in advance, it is still blocked inside the outer sheath because the nitinol wire is too thick. Lasso devices V1, V2, V3, and V4 are shown in Figure 4.4.

Since a different method of cutting is used to prepare stainless steel outer sheathes after lasso-based injection tool V5, the needle moves easier in the outer sheath even with a thicker nitinol wire. Lasso device V5 uses a 127 μm diameter nitinol wire as the lasso loop and it was found that it can grab the CDR more easily than in previous versions. The rotation problem still occurs when stabbing the needle into the port, but the needle has less of a chance to penetrate the whole CDR because it is free to move inside the outer sheath and no additional force is required to push the needle forward. A ground needle and 177.8 μm diameter nitinol wire is tested in the lasso device V6 in which the needle can still move inside the outer sheath. The thicker loop gives additional support

for the loop to reach the end of the lasso guiding gap, and therefore ease the grabbing process. The rotation problem still occurs somehow. Figure 4.5 shows the lasso devices V5 and V6.

Additional layers are put on the nitinol loops in some of the V7 and V8 series of lasso devices. Lasso device V7.1 includes a nitinol loop with silver solder melt on it. However, the high temperature required for the solder (around 180℃ to 190℃ [12]) will destroy the shape of the nitinol loop. The purpose of using solder to assist self-recovery failed. Lasso device V7.2 includes a loop with silver-bended solder melt on it as well, but the solder is applied on the nitinol loop before making the shape of the lasso loop. The grabbing part is effective since the loop can reach the end of the lasso guiding gap, and fix the CDR. However, the rotation problem still occurs. Also, this solder-covered nitinol loop cannot be put into the outer sheath before or after injection because it will remain the same shape after refilling. The nitinol loop has to be inside the outer sheath when the lasso device passes through the 3 mm incision on the cornea.

The Carbothane layer covering the nitinol loop in the lasso device V8.1 enables the loop to recover partially after grabbing. Because the mold for the lasso loop in this version is too small, the loop cannot fit into the mold and take on the desired shape. Therefore, a simple arc is still used and rotation of the CDR during the injection process still occurs. Another problem with this version is that the nitinol loop is too large and firm which makes it difficult to put it back into the outer sheath when necessary.

Though the mold for the lasso loop is enlarged, the nitinol wire in the lasso device V8.2 still has difficulty getting into the mold and forming the desired shape. The result for the arc-shaped loop is that the CDR will rotate when injecting the needle into the port.

New molds are made to achieve the desired shape of the loop to prevent rotation of

the CDR. Figure 5.4 shows the general concept of the desired lasso loops in the lasso device V8 series.

When the loop reaches the end of the lasso guiding gap, two crimps on the loop will fix the port when retracting the lasso loop into the outer sheath. Lasso device V8.3 and V8.4 uses mold V5 (shown in Figure 4.6) to form the desired lasso shape. Though the Carbothane sheets seem to generate a self-recovery loop on the nitinol wire, they are too thick and the loop cannot retract into the outer sheath, which results in failure to grab the CDR.

Lasso device V8.5 uses only the mold and not the Carbothane layers in the V8.4 version. It appears that the device can fully grab the CDR during the injection process. However it has a 50% of chance grabbing the CDR at the wrong angle and thus the needle will penetrate the port in the wrong direction. Figure 5.5 shows the angle between the lasso device and the CDR inside the lens capsule.

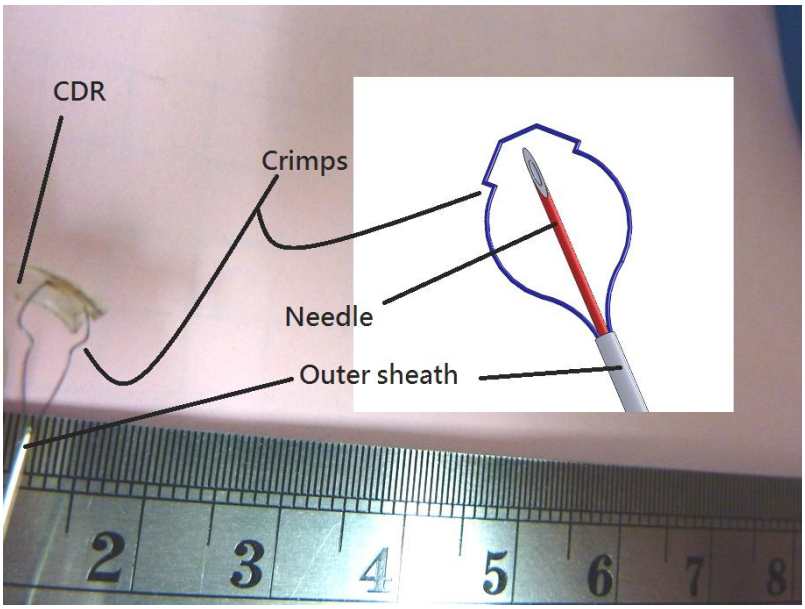


Figure 5. 4 Two crimps on the nitinol loop to prevent the CDR from rotation during the stabbing process

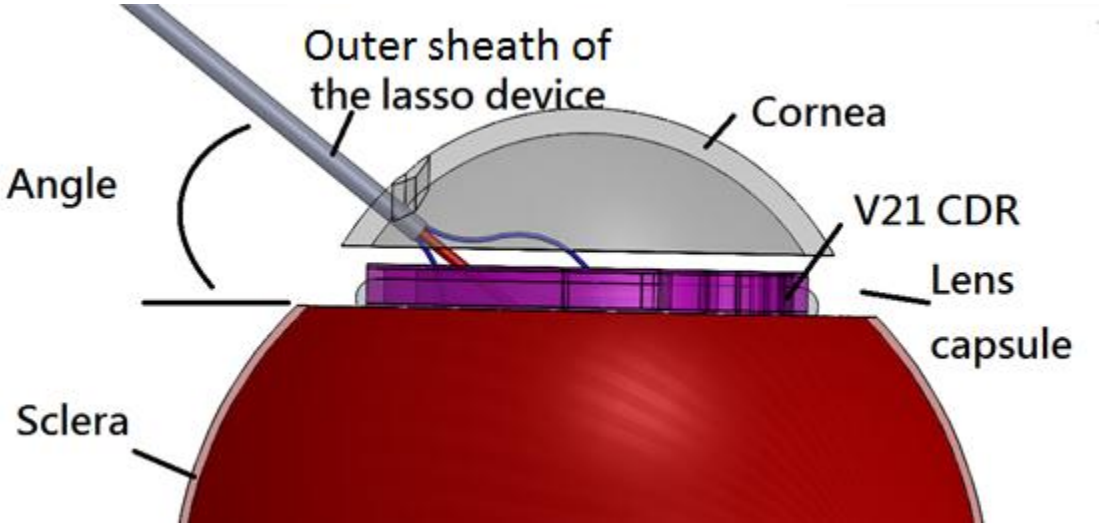


Figure 5. 5 A side view of the V21 CDR and the lasso device inside the lens capsule

The angle between the lasso device and the CDR is assumed to be the same as the one in a 27 gauge cannula (Model: BD Anterior Chamber Cannula 0.40x22 mm 27G x 7/8 in). In order to get direct contact between the outer sheath and the port, the lasso device has to be able to rotate the CDR while pulling the nitinol loop and attempting to grab the CDR.

Lasso device V8.6 can easily go in and out of the lasso guiding gap, and has a 60% chance to make direct contact between the outer sheath and the port when refilling. Though the needle can easily go into the CDR at the port, it is easy for the needle to penetrate through the CDR because it is difficult to control the force applied on the needle. This problem can be fixed by attaching the grabbing device to a piezoelectric actuator because the distance of the needle is preprogrammed.

In order to prevent the CDR from rotating during the injection process, the location of the tip of the needle on the port is discussed and tested. If the tip is injected in the upper or lower parts of the port on the CDR, as shown in the frames A and B in Figure 5.6, the injecting force will balance the rotation force of the CDR. If the needle is

injected into the port as in frame C in Figure 5.6, the injection force will not balance with the rotation force of the CDR, and thus the CDR will rotate out of the plane.

Lasso device V8.7, as shown in Figure 5.7, is designed to eliminate the rotation of the CDR during the injection process. The tip of the injection needle is controlled to make contact with either the bottom or top of the port, as seen in frames A and B in Figure 5.6. The rotation of the CDR can be minimized by this method.

Lasso device V8.8 is a unique design with two different lasso loops, as shown in Figure 5.7. The short loop acts the same as the steps on the longer loop to fix the CDR while retracting the loop back into the outer sheath. Once the CDR is fixed, the injection needle will penetrate the bottom or the top of the port, as shown in frames A and B in Figure 5.6. Though it can lower the possibility for the CDR to rotate during injection, sometimes the CDR will be fixed at the wrong angle and the needle will penetrate through the CDR.

Lasso device series V9 is proposed to make the lasso device and the CDR on the same plane during injection. Figure 5.7 shows lasso device V9.1 with a fix-ended lasso loop. Only one side of the lasso loop can be retracted into the outer sheath and therefore will flip or rotate the CDR by some degrees. This device is able to flip the CDR and achieve a direct contact between the device and the port, but it still needs further modification to achieve a consistent result.

Above all, the common problems for the lasso devices include:

1. The inability of the loop to recover its original shape by itself after grabbing.
2. The rotation of the CDR during the injection process.
3. The existence of the angle between the lasso device and the CDR.
4. The block of needle inside the outer sheath.

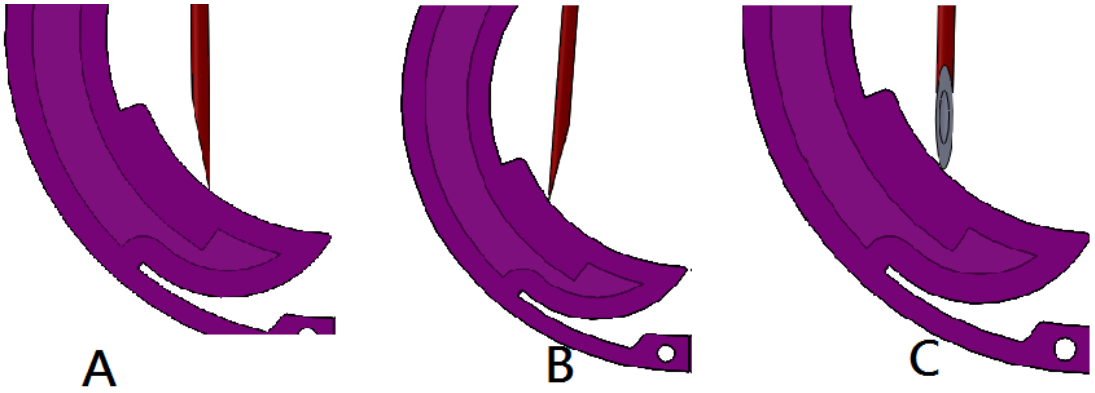


Figure 5. 6 Interface between the needle and the port

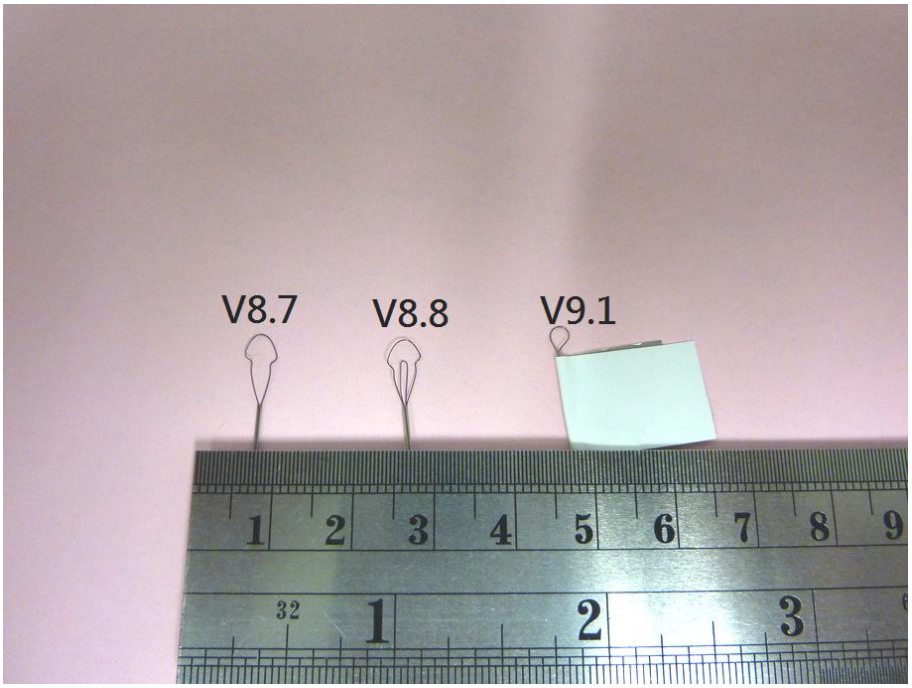


Figure 5. 7 Lasso devices V8.7, V8.8, and V9.1

These problems are solved in some of the versions, but a consistent result has not been fully achieved. At this point, since the lasso tools that solve problem 2 through 4 cannot perform self-recovery, a new loop has to be made for every test and it is difficult to get exactly the same loop every time, making testing difficult and inconsistent.

CHAPTER 6

DESIGN OF OTHER MECHANISMS AND CDRS

Before the lasso-based injection tools were designed and applied to the CDR, several other approaches were tried for securing and injecting drug into the CDR. A summary of some of these efforts is provided in this chapter. Both vacuum-based and grasping or "hand" devices were explored, but eventually rejected for an inability to sufficiently secure the CDR before and during injection.

6.1 Grasping Devices and Their CDRs

The first design tried for securing the CDR in preparation for injection relied on a pair of hands or arms similar to those found in tongs, and look like the lasso-based tools, but with the lasso cut at the tip. The grasping mechanism presented in this work requires a needle, a pair or two pairs of hands, an inner sheath, and, for some versions, an outer sheath. Figure 6.1 shows different versions of grasping devices. Hands or graspers are fixed on the inner sheath, as shown in Figure 6.2. In some versions the hands are dipped with Carbothane because the friction force between two Carbothane pieces (the hand and the CDR) is greater than that between Carbothane and stainless steel or nitinol. Hands can be made from either stainless steel or nitinol. Though nitinol performs self-recovery better than stainless steel, it is softer than stainless steel and has difficulty securing the CDR. Therefore, stainless steel hands are preferred in the grasping devices.

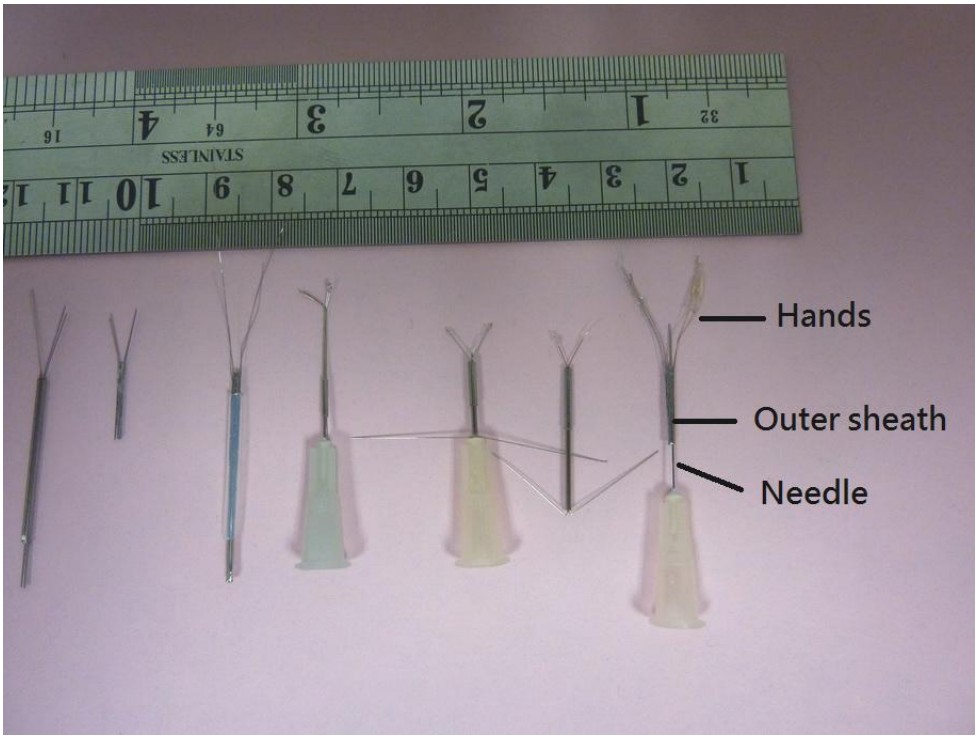


Figure 6. 1 Several grasping devices

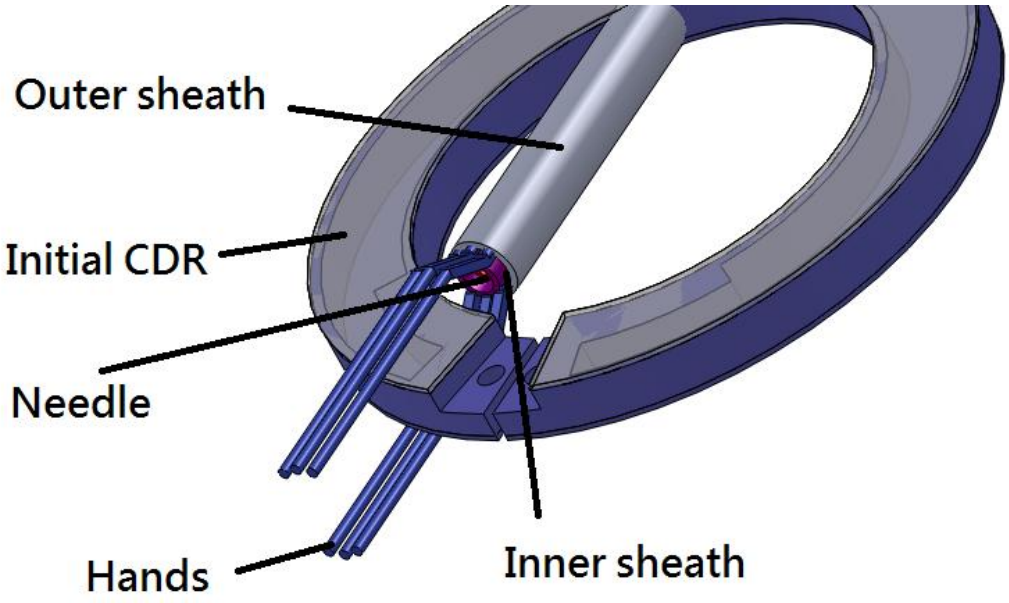


Figure 6. 2 Illustration of a grasping device and an initial CDR

Either 27 gauge or 30 gauge needles are used for injection when the grasping mechanism is used. Some of the design, including an 18 gauge outer sheath, is incompatible with this project due to the limitation of size of the incision on the cornea.

CDRs are not modified to fit the grasping device because a new design was proposed before starting modification of the initial CDR. The new design uses a lasso loop to replace a pair of hands, and this new design became the main design used in this thesis research.

In summary, the drawbacks of the grasping approach are:

1. Hands will scratch the tissue inside the lens capsule when it is longer than the width of the CDR (the difference between the outer radius and the inner radius).
2. Hands shorter than the width of the CDR will have difficulty grabbing the CDR tightly.
3. Attachment of the hands on the inner sheath is difficult, since adhesive is required, and adhesive will block the outer sheath when assembling them together.
4. The angle of the hands is difficult to manipulate into parallel pairs. Thus, the grabbing force is not equal on both sides of the grabbing device and this leads to failure to fix or rotate the CDR.
5. Hands with Carbothane are difficult to pull into the outer sheath.

6.2 Vacuum Tubing Mechanism

A second approach tried before the lasso-based devices used vacuum to pull the CDR into contact with the injection needle. In this system, an outer sheath and an injection needle is used to grab and refill the CDR. Figure 6.3 shows several vacuum grabbing device and CDRs.

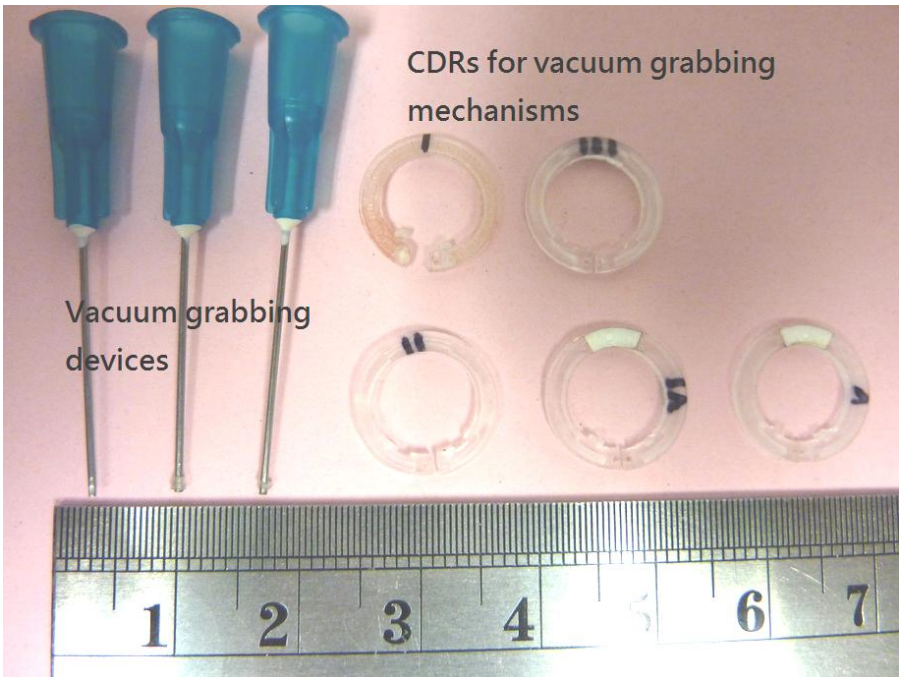


Figure 6. 3 Vacuum grabbing devices and CDRs for vacuum grabbing

When applying vacuum in the vacuum-based devices, the suction force will pick up the CDR at its vacuum port to fix the CDR, as shown in Figure 6.4. Several designs of ports were tested to achieve a better seal between the vacuum-based device and the ports on the CDRs. Additional Carbothane rings are also attached to the outer sheath of the vacuum-based devices to provide extra sealing.

Though the vacuum tubing mechanism is appealing for its simple concept, the suction force is too small to grab the CDR well. Furthermore, the needle has difficulty being assembled into the outer sheath because the entrance of the outer sheath is smaller in diameter than the outer diameter of the needle. In addition, if the device activates before sealing well between the outer sheath and the port, the device will suck the liquid inside the lens capsule and possibly damage the eye or clog the injection needle. Thus, vacuum-based devices were found to be incompatible with the needed design specifications.

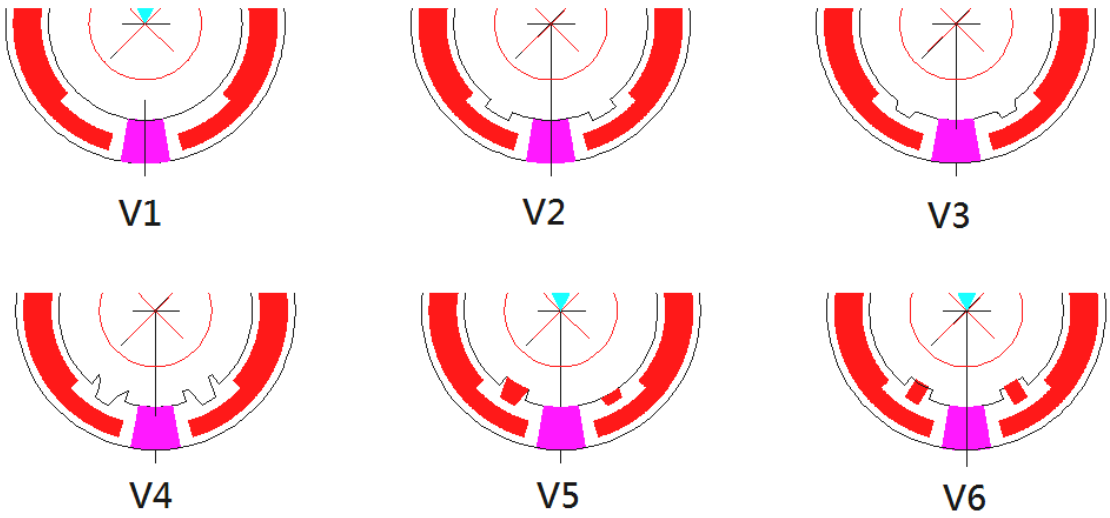


Figure 6. 4 Ports at vacuum-based CDRs

CHAPTER 7

CONCLUSIONS

7.1 Comparison to Functional Specifications

In the beginning of this thesis research, the goal of a refillable CDR was established, and therefore both a refillable CDR and a refilling device were designed to accomplish this purpose. The Appendix provides a checklist comparing the device to the functional specifications for each of the CDRs and the refilling device, respectively.

The latest version of the lasso-based CDR is the V21t04 CDR. It achieves every functional specification, as shown in the Appendix. The latest versions of the lasso grabbing devices are V8.7, V8.8 and V9.1. The reason there are three versions is that they are all different designs, and some of them can be combined into a newer one. Though they achieve many of the functional specifications in the Appendix, there are still several things they have to accomplish before complete success can be declared.

A summary of the achievement of the functional specifications given in Chapter 1 for the lasso-based CDRs is provided below:

1. Biocompatible materials (achieved)
2. Sealing drug reservoir with volume more than 22 μl (achieved)
3. Self-sealing ports (achieved)
4. Dimensional limitation (achieved)
5. Compatibility with and without a filter (achieved)
6. Eyelets (achieved)

7. Easy to be grabbed firmly (achieved)
8. Sufficient injection space for the tip of the needle (achieved)

Achievements of functional specifications of lasso tools are listed below:

1. Biocompatible materials (achieved).
2. 23 gauge outer sheath and 30 gauge injection needle (achieved).
3. Will not scratch the tissue inside the lens capsule (achieved).
4. Firm grabbing (achieved).
5. Avoids axial rotation of the CDR during injection (achieved).
6. Self-recovery lasso loop before refilling (achieved in V9.1).
7. Ability to flip the CDR into the same plane as the grabbing device (achieved in V9.1).
8. A maximum feature smaller than 1.6 mm (not achieved: current size 1.69 mm).

7.2 Contributions

A wide variety of engineering and design contributions were made during the completion of this thesis. For example, this thesis work shows several new ways to grab and refill a CDR. It also demonstrates the usefulness of some guiding mechanisms on the CDR to ease the grabbing process. Additionally, some protective structures on the CDR were shown to prevent potential scratches by the grabbing devices.

With respect to the CDR fabrication, several contributions were made. As a first example, a technique for achieving high quality sidewalls in a laser cut device was developed by introducing an overlap final cut with 50 μm offset from the original boundary for the CDR in every kind of Carbothane sheeting, including 9 separate ones, 9 hot-plated ones, and 10 hot-plated ones. Furthermore, by increasing the thickness of the

sidewall, as accomplished by increasing the gap between two laser ablation areas, the sidewall is able to seal well. Use of the laser also enables the batch fabrication of CDR in every version. The drawing created for the laser also allowed a three-dimensional model to be generated by the machine shop in the Department of Mechanical Engineering for demonstration purposes.

For the grabbing devices, lasso loops are proposed by Dr. Bruce Gale to grab the CDR firmly. In addition, a flipping mechanism is introduced to flip the CDR to get a 90 degree contact between the grabbing device and the port before refilling. What is more, crimps are added to prevent rotation of the CDR while stabbing.

7.3 Future Work

The refillable CDR project is not completed. For the refillable CDR, eyelets at the end of the protection wall (as shown in Figure 2.4) have to be modified to a more rigid structure so that the hook on the Geuder tension ring injector will not destroy the eyelet when grabbing at it.

For the grabbing device, work must be completed to achieve the following specifications:

1. The loop has to be inside the outer sheath before grabbing, and it has to perform self recovery when leaving the outer sheath and starting to grab the CDR.
2. The device has to be able to flip the CDR so that the device has a 90 degree connection with the port of the CDR.
3. If the loop cannot be completely retracted into the outer sheath, the maximum thickness of the loop has to be less than 1.6 mm.

4. The device can be integrated with an automatic controller with one bottom for grabbing and one for refilling.

APPENDIX

Table A.1 Fabrication features of CDRs

CDR ID	Total layer (Start, rest)	Filter	Reservoir	Miscellaneous
V1t48	9 separate, 1, 1	UV treated	2-time raster	
V2t06	9 separate, 1, 1	UV treated	2-time raster	
V3t20	9 separate, 1, 1	UV treated	2-time raster	Overlap reservoir and port area by 150μm
V4t02	9 separate, 1, 1	UV treated	2-time raster	
V5t08	9 separate, 1, 1	n/a	2-time raster	
V6t22	9 separate, 1, 1	UV treated	2-time raster	
V7t16	9 separate, 1, 1	UV treated.	Clear cut	Port area formed by clear cut and 200μm raster.
V8t10	9 separate, 1, 1	n/a	Clear cut	Port area formed by clear cut and 200μm raster.
V9t01 Version1	9 separate, 1, 1	n/a	Clear cut	Port area formed by clear cut and 200μm raster.
V9t01 Version2	9 separate, 1, 1	n/a	Clear cut	Port area formed by clear cut and 200μm raster.
V11t22	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines.
V12t04 Version1	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. 3-time black final cut.

Table A.1 (continued)

CDR ID	Total layer (Start, rest)	Filter	Reservoir	Miscellaneous
V12t04 Version2	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. 2-time black final cut.
V13t19	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. 2-time black final cut.
CDR ID	Total layer (Start, rest)	Filter	Reservoir	Miscellaneous
V14t02	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. 2-time black final cut. Additional 2-time cyan final cut. Additional 1-time yellow vertical cut.
V15t07	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V16t06	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V17t08	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V18t12	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.

Table A.1 (continued)

CDR ID	Total layer (Start, rest)	Filter	Reservoir	Miscellaneous
V19t12	10 separate, 1	n/a	2-time raster	Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V19t15 Version1	9 separate, 1, 1	n/a	Clear cut	Clear cut. Flip and self alignment. Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V19t15 Version2	9 separate, 1, 1	n/a	3-time raster	3-time raster Flip and self alignment. Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V20t05 Version1	9 separate, 1, 1	n/a	2-time raster at the port area, clear cut at the rest.	Peel reservoir before 2-time raster. Combine both 2-time raster and clear cut. Flip and self alignment. Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.

Table A.1 (continued)

CDR ID	Total layer (Start, rest)	Filter	Reservoir	Miscellaneous
V20t05 Version2	9 separate, 1, 1	n/a	2-time raster at the port area, clear cut at the rest.	Peel reservoir after 2-time raster. Combine both 2-time raster and clear cut. Flip and self alignment. Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V21t01 Version1	9 hot-plated, 1, 1	n/a	Clear cut	Hot plate treatment on 9 separate Carbothane sheets. Clear cut. Flip and self alignment. Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V21t01 Version2	10 hot-plated, 1, 1	n/a	Clear cut	Hot plate treatment on 10 separate Carbothane sheets. Clear cut. Flip and self alignment. Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.

Table A.1 (continued)

CDR ID	Total layer (Start, rest)	Filter	Reservoir	Miscellaneous
V21t02	10 hot-plated, 1, 1	n/a	Clear cut	Hot plate treatment on 10 separate Carbothane sheets. Clear cut. Flip and self alignment. Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.
V21t04	10 hot-plated, 1, 1	UV treated.	Clear cut	With filter. Hot plate treatment on 10 separate Carbothane sheets. Clear cut. Flip and self alignment. Extend green and blue lamination lines. Additional cyan and yellow cut such as v14.

Table A.2 Sidewalls of each CDR (unit: micron)

CDR ID	Outer sidewall	Inner sidewall	Port thickness	Top wall	Bottom wall
V1t48	300	300	800	100	100
V2t06	300	300	800	100	100
V3t20	300	300	600	100	100
V4t02	300	300	600	100	100
V5t08	300	300	600	100	100
V6t22	150	150	600	100	100
V7t16	150	150	650 (with 200μm from raster)	100	100
V8t10	150	300	650 (with 200μm from raster)	100	100
V9t01 Version1	150	300	650 (with 200μm from raster)	100	100
V9t01 Version2	150	300	650 (with 200μm from raster)	100	100
V11t22	300	300	350	100	>200
V12t04 Version1	300	300	350	100	>200
V12t04 Version2	300	300	350	100	>200
V13t09	300	300	350	100	>200
V14t02	300	300	350	100	>200
V15t07	300	300	350	100	>200
V16t06	300	300	350	100	>200
V17t08	300	300	900	100	>200
V18t12	300	300	800	100	>200
V19t12	300	300	800	100	>200

Table A.2 (continued)

CDR ID	Outer sidewall	Inner sidewall	Port thickness	Top wall	Bottom wall
V19t15 Version1	450	450	950	100	100
V19t15 Version2	300	300	800	100	100
V20t05 Version1	300@port 450@rest	300@port 450@rest	800	100	>200
V20t05 Version2	300@port 450@rest	300@port 450@rest	800	100	>200
V21t01 Version1	450	450	950	100	100
V21t01 Version2	450	450	950	100	100
V21t02	450	500@filter 450@rest	950	100	100
V21t04	450	500@filter 450@rest	950	100	100

Table A.3 CDR leakage, opening and reservoir volume table

Abbreviation for Table 3.1 and Figure 3.4 (in Chapter 3):
O: outer sidewall. I: inner sidewall. E: entrance. FO: filter (outer). FI: filter (inner).
P: port. G: lasso guiding gap. n/a: loss of CDR model.
X: indicate unavailable for testing due to huge leakages or opening.

CDR ID	Opening	Leakage	Volume
V1t48		O	X
V2t06			18
V3t20		FI	21
V4t02	n/a	n/a	n/a
V5t08		FI, FO	X
V6t22	n/a	n/a	n/a
V7t16	O, FI, G, E		X
V8t10	O, I, FI, FO		X
V9t01 Version1	n/a	n/a	n/a
V9t01 Version2	n/a	n/a	n/a
V11t22 Version1			20
V12t04 Version1	n/a	n/a	n/a
V12t04 Version2	O, FO, P, E		X
V13t09			23
V14t02			18
V15t07			25
V16t06	n/a	n/a	n/a
V17t08			22
V18t12	n/a	n/a	n/a
V19t12			22

Table A.3 (continued)

CDR ID	Opening	Leakage	Volume
V19t15 Version1			29
V19t15 Version2			28
V20t05 Version1		Two leaks	X
V20t05 Version2	O, FO		X
V21t01 Version1			n/a
V21t01 Version2			27
V21t02			32
V21t04			31

Table A.4 Dimension testing (unit: μm)

Specifications	Design	Test 1	Test 2	Test 3
Outer diameter	12400	12300	12330	12280
Inner diameter	8600	8600	8810	8740
Right inner sidewall	500	480	450	90
Right outer sidewall	500	200	250	460
Right port	1000	1050	730	650
Filter inner sidewall	550	220	390	430
Filter outer sidewall	500	420	190	180
Left inner sidewall	500	150	170	530
Left outer sidewall	500	560	380	90
Left port	1000	750	620	900

Table A.5 Checklist for CDRs

Specifications	Check	Applied versions	Check for the latest version (V21t04 CDR)
Sealing drug reservoir	Yes	Most of the versions	Yes
Biocompatible materials	Yes	All.	Yes
Dimensional limitation	Yes	All.	Yes
Compatible with and without a filter	Yes	Most of the versions.	Yes
Self-sealing port	Yes	Some of the vacuum-based versions. Most of the lasso-based versions.	Yes
Eyelets	Yes	All of the vacuum-based versions Most of the lasso-based versions.	Yes
(Optional) Mechanisms to interact with grabbing and refilling devices	Yes	Most of the vacuum-based versions. All of the lasso-based versions.	Yes
Volume of the drug reservoir achieves around 30 microliters	Yes	Some of the lasso-based versions	Yes

Table A.6 Checklist for grabbing devices

Specifications	Check	Applied versions	Check for the latest versions (V8.7, V8.8 and V9.1)
Biocompatible materials	Yes	All	Yes
23 gauge outer sheath	Yes	Most of the lasso grabbing devices	Yes
30 gauge injection needle	Yes	All of the lasso grabbing devices	Yes
Will not scratch the tissue inside the lens capsule	Yes	All of the lasso grabbing devices	Yes
Firm grabbing	Yes	All of the lasso grabbing devices	Yes
Prevention of CDR rotation while stabbing	Some	Some of the lasso grabbing devices	Yes
Maximum feature size smaller than 1.6 mm (for 2.4 mm incision)	Some	Some of the lasso grabbing devices. For V8.5, the width for the loop is 1.69 mm	No.
Self-recovery nitinol loop before refilling	Some	Some of the lasso grabbing devices.	Yes for V9.1. No for v8 series.
Able to flip the CDR into the same plane as the grabbing device	Some	V9.1	Yes for V9.1 No for all the rest.

Table A.6 (continued)

Specifications	Check	Applied versions	Check for the latest versions (V8.7, V8.8 and V9.1)
(Optional) Self-recovery nitinol loop after refilling	Some	Some of the lasso grabbing devices	Yes for V9.1. No for the V8 series.
Automatic control of grabbing and refilling	No	No	No

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